A general catalytic β-C–H carbonylation of aliphatic amines to β-lactams

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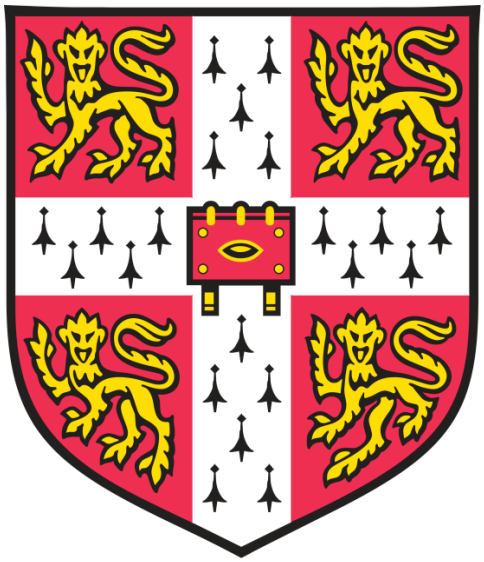

This dissertation is submitted for the Degree of Doctor of Philosophy

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i Declaration

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes the work carried out in the Department of Chemistry from October 2013 to September 2017. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

Ben Chappell
September 2017

ii Statement of Length

This dissertation does not exceed the word limit of 60 000 as set by the Degree Committee for the faculty of Physics and Chemistry.

Ben Chappell
September 2017

iii Acknowledgements

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Finally, I would like to thank everyone that has supported me throughout this PhD; without you, this would not have been possible.

iv Abbreviations

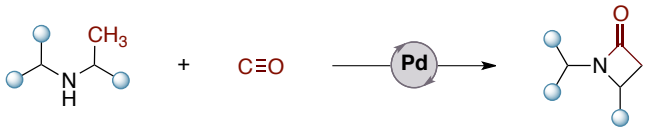
Å	angstrom
°C	degrees celcius
δ	chemical shift
Δ	heat or difference
Ac	acetyl
Ad	1-adamantane
ADF	Amsterdam density functional software package
APCI	atmospheric pressure chemical ionisation
app	apparent multiplicity
aq.	aqueous
Ar	aryl
atm	atmospheres
ATR	attentuated total reflectance
BLYP-D3	Becke, Lee, Yang, Parr exchange correlation, with the third generation Grimme dispersion correction
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
BQ	1,4-benzoquinone
br	broad
^{n}Bu	normal butyl
^{t}Bu	tertiary butyl
c	concentration
calcd.	calculated
CAN	ceric ammonium nitrate
CBz	carboxybenzyl
cm^{-1}	wavenumbers
CMD	concerted metalation deprotonation
conc.	concentrated
COSMO	conductor like screening model
COSY	homonuclear correlation spectroscopy
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
decomp.	decomposed
DEPT135	distortionless enhancement by polarisation transfer, Φ_3 flip angle of 135°
DFT	density functional theory
DG	directing group

DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOSY	diffusion ordered spectroscopy
d/r	diasteromeric ratio
DZP	double zeta plus polarisation basis set
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
FID	flame ionisation detector
GC	gas chromatography
h	hour(s)
HFIP	hexafluoro*iso*propanol
HMBC	heteronuclear multiple-bond correlation spectroscopy
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single-quantum correlation spectroscopy
IR	infrared
kcal	kilocalorie
KIE	kinetic isotope effect
L	generic two electron ligand
m	meta
m	multiplet
Me	methyl
Men	menthyl
Mes	mesityl
min	minute(s)
MOM	methyloxymethyl
m.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
Nu	nucleophile
nOe	nuclear Overhauser effect
NSI	nanospray ionisation
p	para
Ph	phenyl
Piv	pivaloyl or pivalate
PMB	paramethoxybenzene
PMP	paramethoxyphenyl
ppm	parts per million
Pr	propyl
^{i}Pr	isopropyl
Pthal	phthalimide

q	quartet
qn	quintet
quant.	quantitative
R	generic alkyl
R_f	retention factor
RPM	rotations per minute
rt	room temperature
s	singlet
S_EAr	electrophilic aromatic substitution
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCE	1,1,2,2-tetrachloroethane
TEMPO	2,2,6,6,-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid or trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
TZ2P	triple zeta plus double polarisation basis set
UFF	universal forcefield
v/v	volume/volume
X	generic one electron ligand
XC	exchange correlation
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

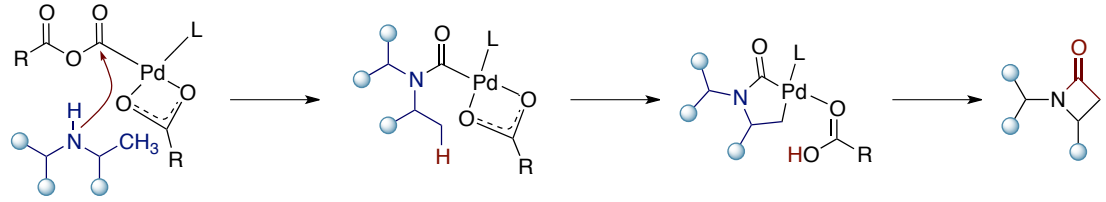
v Abstract

Carbonyl compounds are of central importance to organic chemistry and their reactions have been described as the 'backbone of organic synthesis'. Over recent decades, palladium-catalysed C–H carbonylation reactions have emerged as a powerful means of introducing carbonyl motifs to organic molecules. This thesis describes the development of a general C–H carbonylation reaction of secondary aliphatic amines, which provides facile access to synthetically useful β-lactam products.



The first part of the thesis explores the scope and limitations of this reaction. Whilst previous C(sp^3)–H carbonylation methodologies were restricted to 'Type F' secondary aliphatic amines, the reaction described in this thesis was found to be broadly applicable all structural sub-classes of secondary aliphatic amine. Furthermore, the reaction was found to be remarkably tolerant of functional groups, even those that commonly cause issues in palladium-catalysed C–H activation reactions such as heteroaromatics and thioethers.

The second part of this thesis investigates the mechanism of this C–H carbonylation reaction. Interestingly, the reaction was found not to proceed *via* a traditional C–H carbonylation mechanism comprising of C–H activation, 1,1-migratory carbon monoxide insertion and reductive elimination. Instead, a new mechanistic paradigm for palladium-catalysed C–H carbonylation is proposed, which invokes a putative 'palladium anhydride' intermediate. A series of DFT calculations and experiments were conducted in order to support this mechanistic proposal. The work described within this PhD thesis was published in *Science*.



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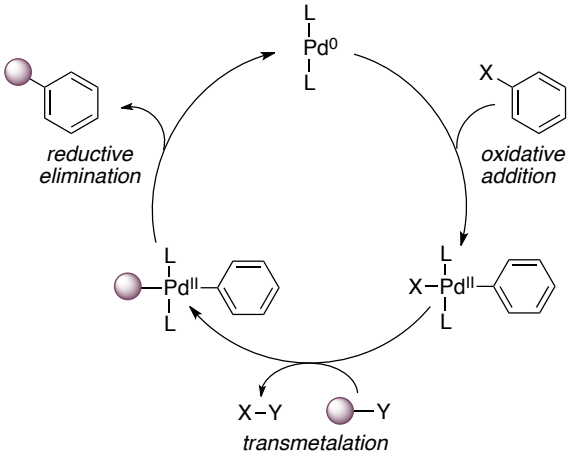
1. Introduction to palladium-catalysed C–H carbonylation

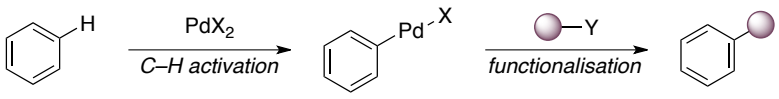
1.1 Key concepts in palladium catalysed C–H functionalisation

Organopalladium chemistry has fundamentally changed the way that organic chemists approach synthesis.[1] Intermediates containing Pd–C bonds have been used to forge a myriad of bonds to carbon, including carbon–carbon,[2] carbon–nitrogen,[3] carbon–sulfur,[4] carbon–oxygen,[5] carbon–phosphorous,[6] carbon-fluorine[7] and many others. Reactive organopalladium intermediates are most commonly accessed by oxidative addition of palladium(0) into a carbon–halogen (or carbon–pseudohalogen) bond. The subsequent derivatisation of these organopalladium complexes by transmetalation followed by reductive elimination forms the basis of palladium-catalysed cross coupling methodology, which was awarded the 2010 Nobel prize in chemistry (Scheme 1).[8] Although other transition metals have been shown to catalyse cross coupling reactions, palladium-catalysed processes are, by far, the most popular[8] and are routinely employed in the synthesis of pharmaceuticals,[9] agrochemicals[9] and optoelectronics.[10]



Scheme 1: The mechanism of palladium-catalysed cross coupling reactions.

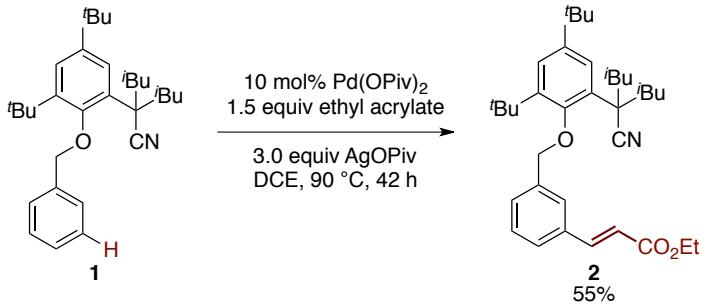
Whilst the importance of cross coupling chemistry cannot be overstated, the methodology is fundamentally limited by the requirement of a starting material that has been prefunctionalised with a carbon-halogen bond. As a result of this, palladium-catalysed cross coupling chemistry can only be employed to functionalise positions of organic molecules that are already within the reach of organic chemistry. An increasingly popular method for accessing organopalladium intermediates is *via* C–H activation, which furnishes a Pd–C bond directly from a C–H bond. The broad chemistry of the organopalladium intermediates formed by C–H activation can then be exploited in a functionalisation step, providing access to a diverse range of products. Taken together, a C–H activation step followed by a functionalisation step constitutes a C–H functionalisation reaction, which is illustrated in Scheme 2.



Scheme 2: A generic C–H functionalisation reaction, comprising of a C–H activation step and a functionalisation step.

Accessing organopalladium intermediates by C–H activation confers a significant advantage; the starting materials do not require prefunctionalisation. This allows the creation of Pd–C bonds at positions of

organic molecules that are difficult or impossible to functionalise using traditional organic chemistry. C–H activation chemistry thus allows the development of new disconnections within synthesis and could, arguably, revolutionalise the way organic chemists make molecules. An illustrative example of an unusual disconnection is provided by Yu's palladium catalysed *meta*-alkenylation of arenes (Scheme 3).[11] Whilst traditional electrophilic aromatic substitution chemistry would readily functionalise the *ortho* and *para* positions of **1**, the *meta* position would be inaccessible to this chemistry.



Scheme 3: Yu's *meta* C–H alkenylation of arenes

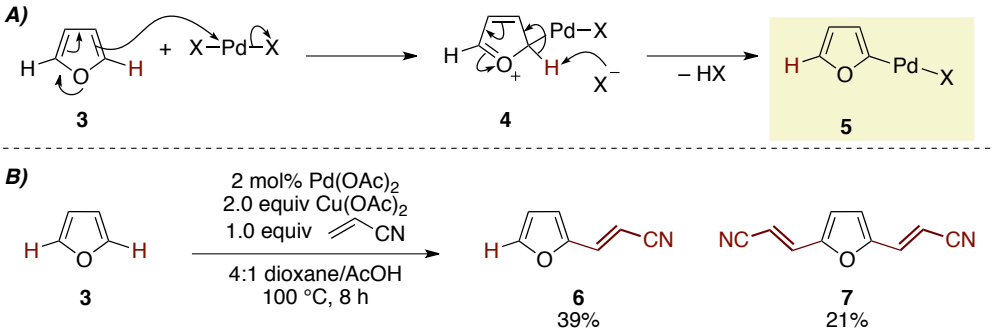
To aid understanding of palladium-catalysed C–H functionalisation reactions, the remainder of the introduction is divided into two sections. Initially, access to organopalladium intermediates *via* C–H activation is discussed in Section 1.2 and the derivatisation of the resulting organopalladium intermediates is discussed in Section 1.3. C–H functionalisation reactions catalysed by other transition metals are beyond the scope of this introduction, accordingly the reader is referred to the following reviews for further information.[12–18]

1.2 Strategies to achieve site selective C–H activation

Organic molecules can be succinctly described as scaffolds of consecutive carbon atoms that are capped with hydrogen atoms and decorated with occasional heteroatoms (mainly oxygen, nitrogen, phosphorous, sulfur and the halogens).[19] C–H bonds are, thus, ubiquitous in organic molecules and the consideration of a C–H bond as a reactive moiety offers a bounty of opportunity for complex molecule synthesis. Whilst the ubiquity of C–H bonds within organic molecules provides opportunity, it also presents a critical selectivity challenge; if a reaction resulted in every C–H bond of an organic molecule undergoing unselective C–H activation, an intractable reaction mixture would result. An ideal C–H activation would, therefore, successfully target a single C–H bond within an organic molecule, producing a single functionalised product. Fortunately, a number of strategies have been developed that allow selective palladium mediated C–H activation.[20] These strategies can be largely divided into three main categories: electronic control, steric control or directing group control. To aid future discussion of C–H activation reactions, each of these strategies will be examined, briefly, in turn.

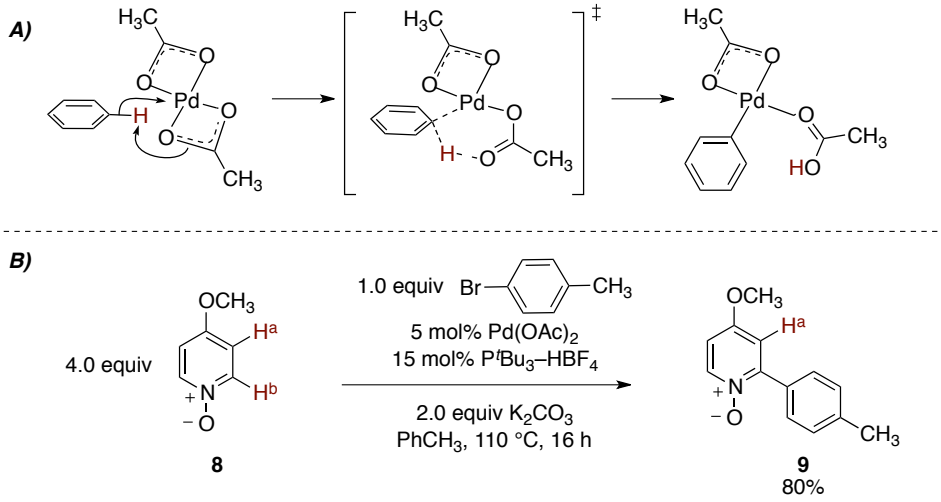
1.2.1 Electronic control of C–H activation

Palladium(II) complexes are electrophilic and, accordingly, can experience attack by arene nucleophiles to provide arenium ions (**4**, Scheme 4, A). The resulting arenium ions can then undergo facile deprotonation to provide σ-aryl palladium complexes (**5**). This mechanism of C–H activation is referred to as electrophilic aromatic substitution (S_EAr) and is particularly common for electron rich heterocycles such as furan, thiophene and indole. The first examples of palladium catalysed C–H functionalisations by an S_EAr mechanism were detailed by Fujiwara (Scheme 4, B).[21]



Scheme 4: C–H functionalisation of electron rich arenes by an electrophilic aromatic substitution (S_EAr) mechanism. **A)** The S_EAr mechanism of C–H activation; **B)** Fujiwara's catalytic C–H alkenylation of furans by an S_EAr mechanism.

In addition to S_EAr pathways, a second C–H activation mechanism is commonly exploited using palladium catalysts, which involves the concerted deprotonation of a C–H bond and metalation of the carbon. This concerted metalation deprotonation (CMD) mechanism (Scheme 5, A) targets the most acidic C–H bond within a substrate and induces reaction at the most electron poor positions of arenes.[22] This mechanism was exemplified by Fagnou in the C–H arylation of *N*-methoxypyridinium *N*-oxide **8**, which proceeded *via* activation of the most acidic C–H bond (Scheme 5, B).[23]



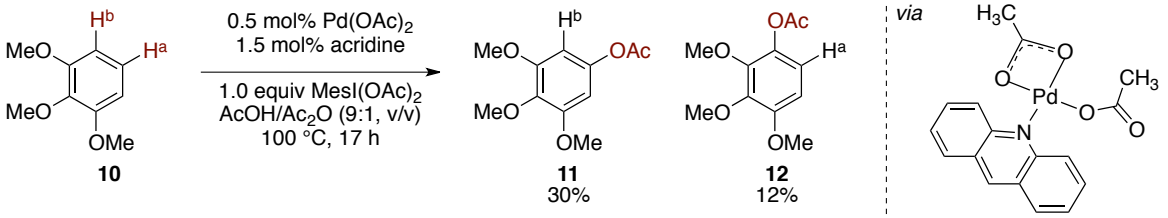
Scheme 5: C–H functionalisation of arenes by a concerted metalation deprotonation (CMD) mechanism. **A)** The CMD mechanism of C–H activation; **B)** Fagnou's catalytic C–H arylation of pyridinium *N*-oxides by a CMD mechanism.

To summarise, the electronic properties of molecules can be exploited to achieve selective C–H activation. Electrophilic aromatic substitution (S_EAr) mechanisms target the most electron rich C–H bonds within aromatic molecules. Conversely, a concerted metalation deprotonation (CMD) mechanism can be leveraged to selectively functionalise the most acidic C–H bonds within substrates. These two mechanisms of palladium mediated C–H activation provide complementary reactivity and can be exploited to achieve selective C–H activation.

1.2.2 Steric control of C–H activation

Whilst electronically controlled palladium-catalysed C–H activation reactions are common, reports of sterically controlled palladium-catalysed processes remain rare.[24,25] However, it is important to note that the steric properties of molecules can be an important factor in palladium mediated C–H activation. An illustrative example was described by Sanford in the C–H acetoxylation of arene **10** (Scheme 6), which

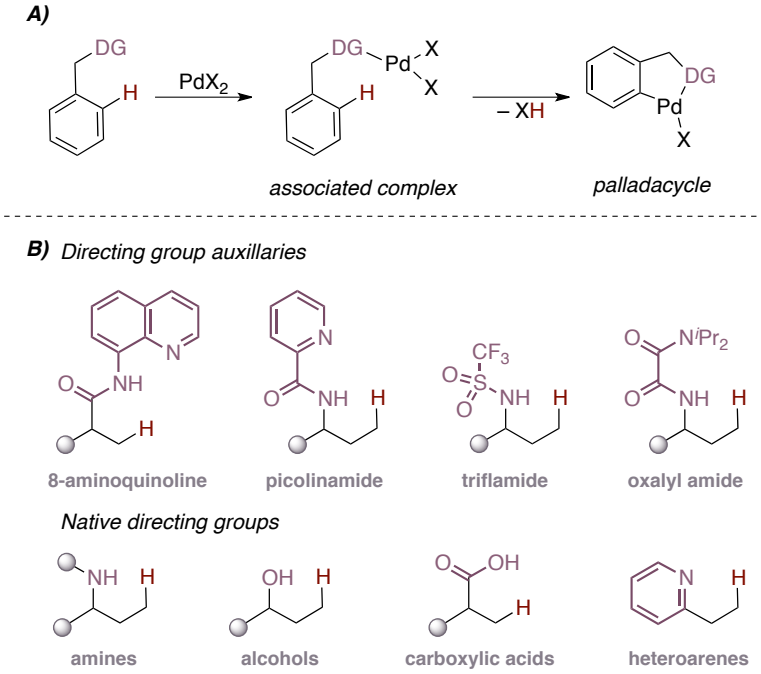
would be expected to proceed *via* an S_EAr mechanism. Of the two C–H bonds that could be activated, C–H^b is more electron rich, whereas C–H^a is more sterically accessible. Sanford's C–H acetyoxylation reaction employs an acridine ligand, which associates to the palladium centre to afford a sterically encumbered palladium catalyst (Scheme 6, right). The reactivity of this palladium catalyst is dominated by steric interactions, thus the inherent electronic bias of arene **10** is overridden and preferential activation of the less electronically activated, but sterically more accessible, C–H^a bond is observed.



Scheme 6: Sanford's sterically controlled C–H acetoxylation of arenes.

1.2.3 Directing group control of C–H activation

By far the most popular approach to achieving site selective C–H activation involves the use of a 'directing group' (Scheme 7, A). A directing group binds to palladium, typically by virtue of one or more Lewis basic heteroatoms, and positions the metal catalyst near a specific C–H bond such that C–H activation can proceed by cyclometalation. The cyclometalation process is extremely sensitive to ring size, with five-membered palladacycles typically being kinetically favoured over other ring sizes.[26,27]



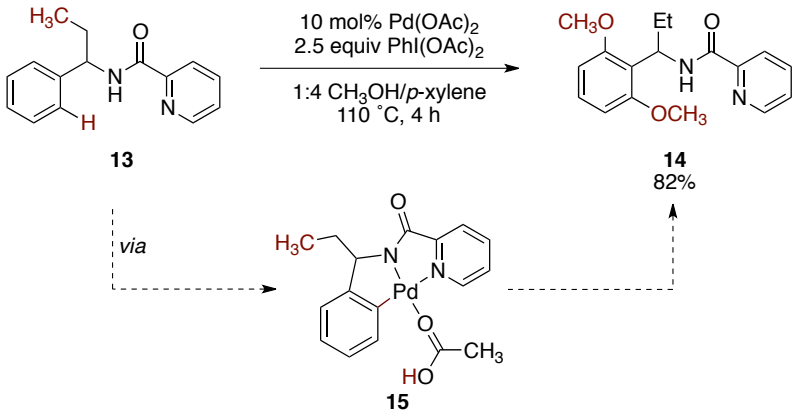
Scheme 7: Directing group controlled C–H activation. **A)** Control of C–H activation by proximity to the directing group; **B)** Common directing groups in palladium–catalysed C–H activation

There are two main classes of directing groups for palladium C–H functionalisation reactions; directing group auxiliaries and native directing groups (Scheme 7, B). Directing group auxiliaries are bespoke moieties that are covalently attached to a specific functional group within a substrate. Auxiliary directed C–H activation is remarkably reliable and is popular within the field of C–H activation.[28] However, the additional synthetic steps required to install and remove a directing group auxiliary represents a significant disadvantage of this strategy. With the aim of streamlining C–H functionalisation reactions, a

number of research groups have more recently focused on developing 'native directing group' strategies for catalytic C–H functionalisation.[29] To date, a number of functional groups that are commonly found in organic molecules have been shown to direct C–H activation, such as alcohols,[30] carboxylic acids[31] and amines.[32,33]

1.2.4 C(sp^3)–H activation vs. C(sp^2)–H activation

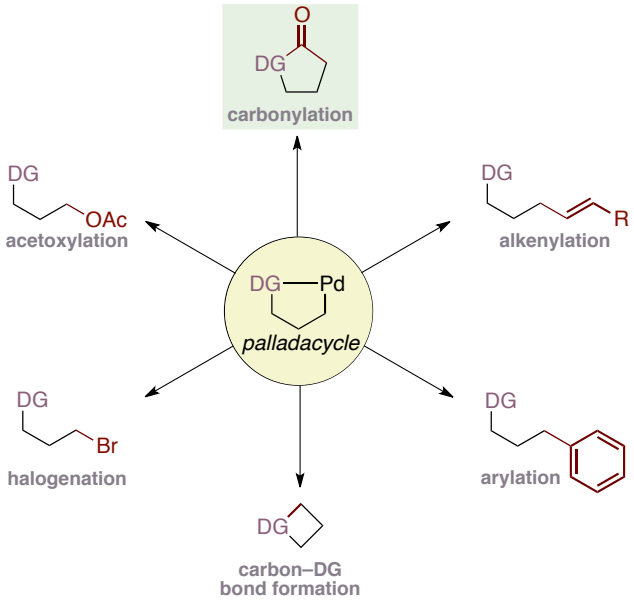
A final consideration with regards to achieving selectivity in C–H activation is the relative ease of activation of C(sp^3)–H and C(sp^2)–H bonds. C(sp^2)–H bonds are stronger than C(sp^3)–H bonds, with relative bond dissociation energies of 106 kcal/mol and 104 kcal/mol respectively.[34] However, C(sp^2)–H bonds are significantly easier to activate using palladium catalysts than C(sp^3)–H bonds due to stabilising interactions between π orbitals of the C(sp^2) framework and d orbitals of the palladium catalyst.[35] The relative ease of C(sp^2)–H activation over C(sp^3)–H activation allows the activation of C(sp^2)–H bonds to be carried out selectively in the presence of C(sp^3)–H bonds as exemplified by Chen (Scheme 8).[36]



Scheme 8: An illustrative example of the preference for C(sp^2)–H activation over C(sp^3)–H activation

1.3 An introduction to C–H carbonylation

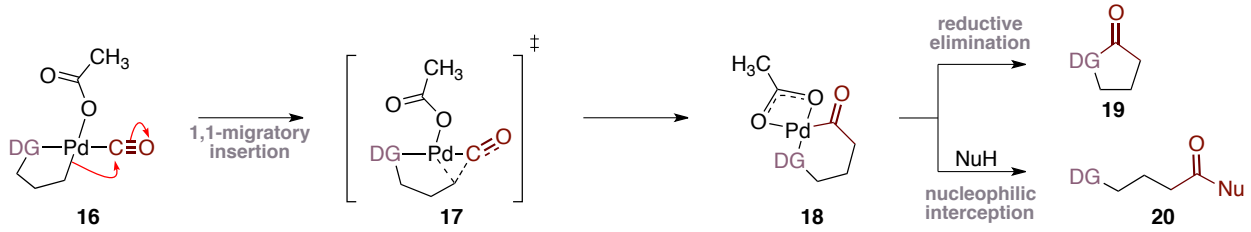
The organopalladium complexes resulting from C–H activation can undergo a diverse array of functionalisation reactions (Scheme 9).



Scheme 9: Common functionalisation reactions of organopalladium intermediates

Perhaps one of the most powerful functionalisation reactions is carbonylation, which involves the reaction of an organopalladium complex with carbon monoxide to form a carbonylated product.[37] C–H carbonylation provides direct access to versatile carbonyl containing products from simple starting materials. Indeed, the importance of carbon compounds is such that carbonyl chemistry has been famously described as the "backbone of organic synthesis".[38]

The mechanism of organopalladium complex carbonylation involves coordination of carbon monoxide, followed by a 1,1-migratory insertion to provide an acyl complex **18** (Scheme 10).[39] The acyl palladium complex **18** can then undergo, either, a reductive elimination[40] (Scheme 10, top) or be intercepted with nucleophiles[41,42] (Scheme 10, bottom) to afford carbonylated products.



Scheme 10: The generally accepted mechanism for carbonylation of organopalladium intermediates

In addition to the chemoselectivity and regioselectivity challenges that plague all C–H functionalisation reactions, C–H carbonylation reactions possess their own unique challenges and as such, are widely accepted to be difficult to achieve.[43] The facile reduction of palladium(II) complexes under a carbon monoxide atmosphere is one such challenge.[44] As a result, there is a requirement for a catalytic C–H carbonylation process to be kinetically competitive with carbon monoxide mediated catalyst degradation. Additionally, carbonylation reactions can be hampered by the low solubility of carbon monoxide in organic solvents.[45–47]

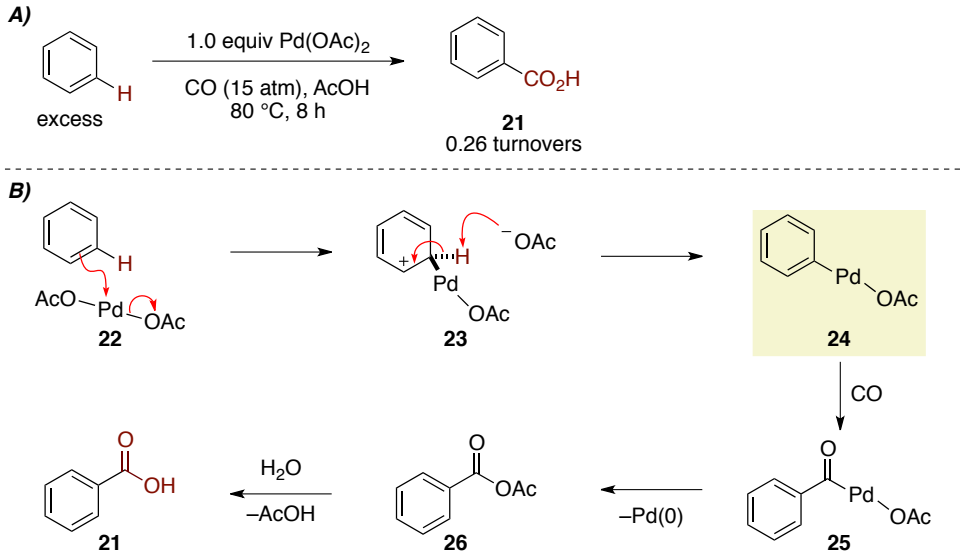
The remainder of this introduction will review palladium-catalysed C–H carbonylation reactions, with a focus on the mechanisms of these processes. Similar to other C–H functionalisation reactions, the overwhelming majority of reported palladium-catalysed C–H carbonylations now employ a directing group to ensure site selective C–H activation,[27] however, this is a more recent phenomenon. The earliest examples of palladium-catalysed C–H carbonylation reactions employed alternative strategies to control site selectivity.[48] Accordingly, these early strategies will first be discussed, before turning to review more recent examples of directing group enabled C–H carbonylation.

1.4 Directing group free C(sp^2)–H carbonylation

1.4.1 Early work towards the development of palladium-catalysed C–H carbonylation

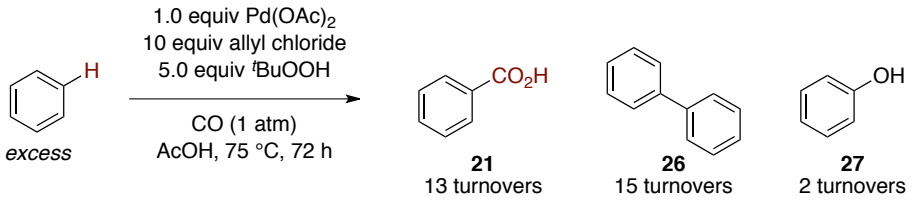
Throughout the 1980s and 1990s, Fujiwara made a number of pioneering discoveries that culminated in the first examples of palladium-catalysed C–H carbonylation reactions. In the first report of the series, Fujiwara disclosed the direct palladium-mediated C–H carbonylation of simple arenes to provide benzoic acids (Scheme 11, A). In analogy to previous work on the C–H alkenylation of arenes by the same laboratory,[49] Fujiwara proposed that arenes could undergo C–H activation by an S_EAr mechanism to provide aryl palladium σ-complexes (**24**, Scheme 11, B).[48] Fujiwara recognised that carbon monoxide coordination to these organopalladium complexes, followed by 1,1-migratory insertion would lead to an

acyl-palladium complex **25**, from which reductive elimination would provide an organic anhydride (**26**). Subsequent hydrolysis of this anhydride under the reaction conditions furnished a benzoic acid product.[48] The mechanistic blueprint put forward by Fujiwara in this study was very influential and has underpinned the overwhelming majority of subsequent C–H carbonylation reactions with palladium(II) catalysts.



Scheme 11: Fujiwara's C(sp^2)–H carbonylation of arenes. **A)** The C(sp^2)–H carbonylation of benzene; **B)** Fujiwara's proposed mechanism.

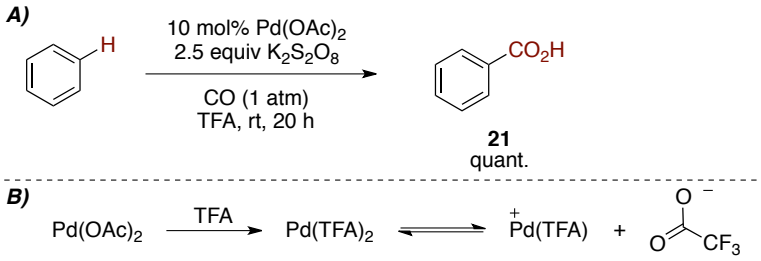
Whilst this work represents an important conceptual advance, the synthetic utility of Fujiwara's initial C–H carbonylation methodology was severely limited; the reaction utilised stoichiometric palladium acetate, excess substrate and provided poor yields of benzoic acid **21**. Fujiwara notes in a later publication that the carbon monoxide mediated reduction of the palladium(II) catalyst, resulting in palladium black, was a significant issue in these initial studies.[50] Subsequent research in Fujiwara's laboratory improved the synthetic utility of this C–H carbonylation procedure. An early improvement employed ^{t}BuOOH and allyl chloride oxidants, which made the C–H carbonylation catalytic in palladium(II).[51] Unfortunately, in addition to the desired benzoic acid (**21**) product, these reaction conditions led to the generation of significant quantities of biphenyl (**26**) and phenol (**27**) side products.



Scheme 12: Fujiwara's first catalytic C(sp^2)–H carbonylation of benzene

Further work led to the discovery that a $K_2S_2O_8$ oxidant enabled palladium catalysis without the formation of arene-derived side products.[50] Significantly, Fujiwara also determined, for the first time, that the arene substrate could be used as the limiting reagent in the C–H carbonylation reaction (Scheme 13, A). Pivotal to the success of Fujiwara's new C–H carbonylation conditions was the *in situ* generation of a $Pd(TFA)^+$ active catalyst from the reaction of palladium acetate and the trifluoroacetic acid (TFA) solvent (Scheme 13, B). The extremely electrophilic $Pd(TFA)^+$ complex is readily intercepted by arenes and results in an acceleration of the C–H bond cleavage event.[52] These reaction conditions enable the C–H carbonylation

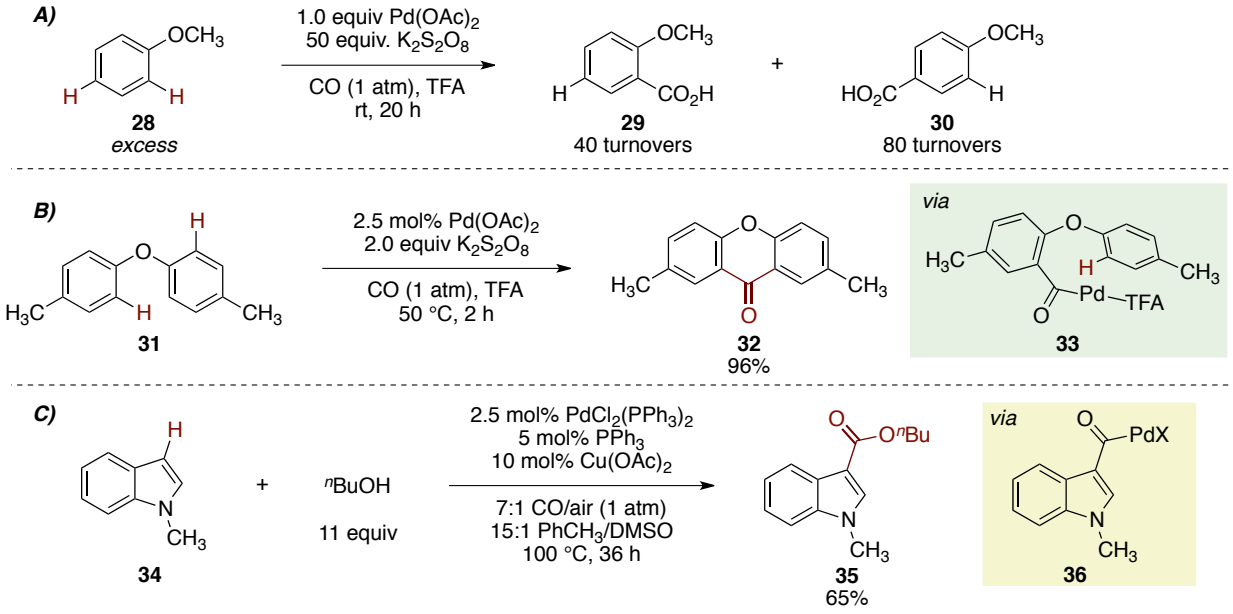
reaction to successfully outcompete the deleterious catalyst reduction that had beleaguered earlier reactions.[50]



Scheme 13: Fujiwara's improved C–H carbonylation procedure. **A)** The catalytic C(sp^2)–H carbonylation of benzene; **B)** The formation of cationic $Pd(TFA)^+$ species from $Pd(OAc)_2$ and TFA.

1.4.2 Regioselective C–H carbonylation controlled by the substrate's electronic properties

Fujiwara demonstrated that the electronic properties of substituted arenes could be exploited to control the regioselectivity of a C–H carbonylation reaction (Scheme 14, A).[50] Whilst Fujiwara's C–H carbonylation was completely selective for electron rich positions (*ortho* and *para*) over electron poor positions (*meta*), the reaction did not fully discriminate between electron rich positions and thus a mixture of regioisomeric products resulted. Lei built upon this work and employed *para* blocking groups to achieve the selective double *ortho* C–H carbonylation of diaryl ethers to furnish xanthones (Scheme 14, B).[53] Lei proposed an initial C–H activation by an S_EAr mechanism of **31**, followed by carbon monoxide insertion provided acyl palladium complex **33**. It was then suggested that acyl palladium complex **33** underwent a second *ortho* C–H activation event to provide a seven-membered palladacycle, from which reductive elimination furnished xanthone product **32**.



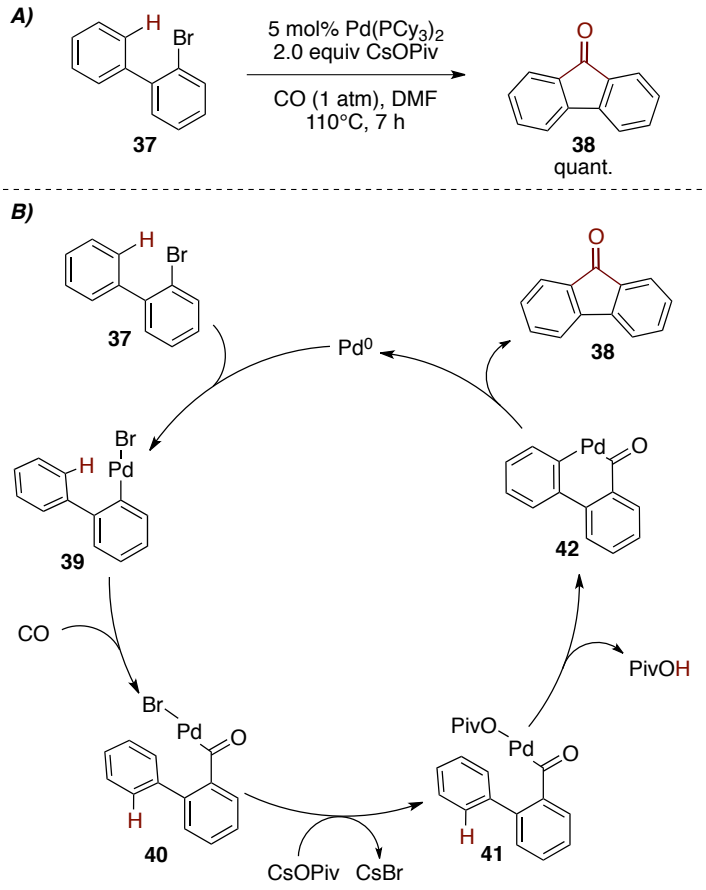
Scheme 14: Electronic control of C(sp^2)–H carbonylation. **A)** Fujiwara's catalytic C(sp^2)–H carbonylation of anisole; **B)** Lei's xanthanone synthesis by C(sp^2)–H carbonylation; **C)** Lei's C(sp^2)–H carbonylation of indoles.

Finally, Lei revealed that *N*-methylindoles were amenable to C–H carbonylation and that the reaction was selective for the most electron rich C3 position[54] (Scheme 14, C).[55] C3 selective C–H activation of the heteroaromatic, followed by carbon monoxide insertion was surmised to lead to an acyl palladium complex **36**, which could be intercepted by nucleophiles to provide carbonylated products. Reaction

conditions were developed that allowed both alcohol[55] and amine[56] nucleophiles to be employed in the C–H carbonylation reaction, providing access to ester and amide products respectively.

1.4.3 Regioselective C–H carbonylation controlled by a prior oxidative addition

Shortly after Fujiwara's seminal studies on electronically controlled C–H carbonylations,[50] Larock communicated the C–H carbonylation of *ortho*-halogenated biaryls to provide fluoren-9-ones (Scheme 15, A). Larock's methodology is conceptually distinct to that pioneered by Fujiwara as it relies upon an oxidative addition step to precisely position the palladium metal within the substrate.[57] The regiochemistry of the subsequent C–H activation step is then controlled by proximity to the site of oxidative addition. Whilst this strategy is elegant, the use of oxidative addition requires a prefunctionalised site on the substrate, which is a limitation of the methodology. The mechanism of the reaction was suspected to involve the oxidative insertion of palladium(0) into the C–Br bond of the substrate, which, after carbon monoxide coordination and 1,1-migratory insertion, leads to acyl palladium complex **40** (Scheme 15, B). Following ligand substitution, C–H activation was believed to provide six-membered palladacycle **42**. The necessity of a bulky pivalate base in the reaction suggests that the C–H activation event proceeds *via* a CMD mechanism.[58] Finally, reductive elimination from the palladacycle **42** furnished fluoren-9-one **38** and regenerates the palladium(0) catalyst.



Scheme 15: Larock's C(sp^2)–H carbonylation controlled by oxidative addition. **A)** The catalytic C–H carbonylation of ortho-bromo biaryls; **B)** Larock's proposed mechanism

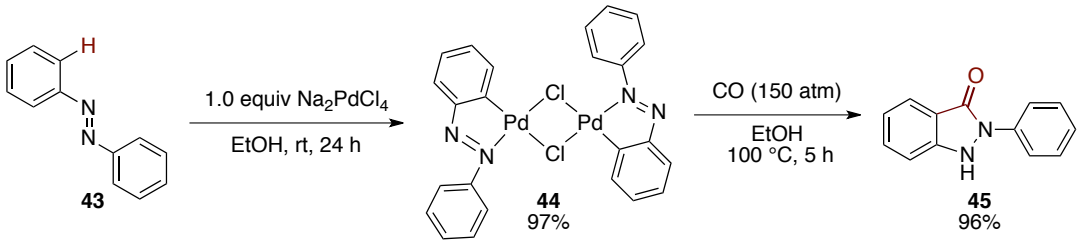
1.4.4 Summary of directing group free C–H carbonylation

In summary, there are two main strategies for achieving selective directing group free C–H carbonylation. Firstly, C–H activation can occur *via* an S_EAr mechanism and selectivity for the most electron rich positions of aromatic rings is observed. The regioselectivites obtained in these S_EAr C–H activation reactions thus closely mirror the selectivities observed in traditional electrophilic aromatic substitution reactions.[59] Secondly, oxidative addition of a palladium(0) catalyst into a carbon–halogen bond within a substrate allows the precise positioning of palladium within a molecule. Following carbon monoxide insertion, a C–H bond proximal to the site of oxidative addition can then undergo a selective C–H activation and ultimately furnish a carbonylated product.

1.5 Directing group-enabled C–H carbonylation

1.5.1 C(sp^2)–H carbonylation reactions

In 1967, Tsuji described the first stoichiometric example of a directed C–H carbonylation reaction mediated by palladium.[60] Azobenzene **43** was shown to undergo selective *ortho* C–H activation to provide dimeric palladacycle **44**, which when treated with carbon monoxide furnished indazolinone **45** (Scheme 16).

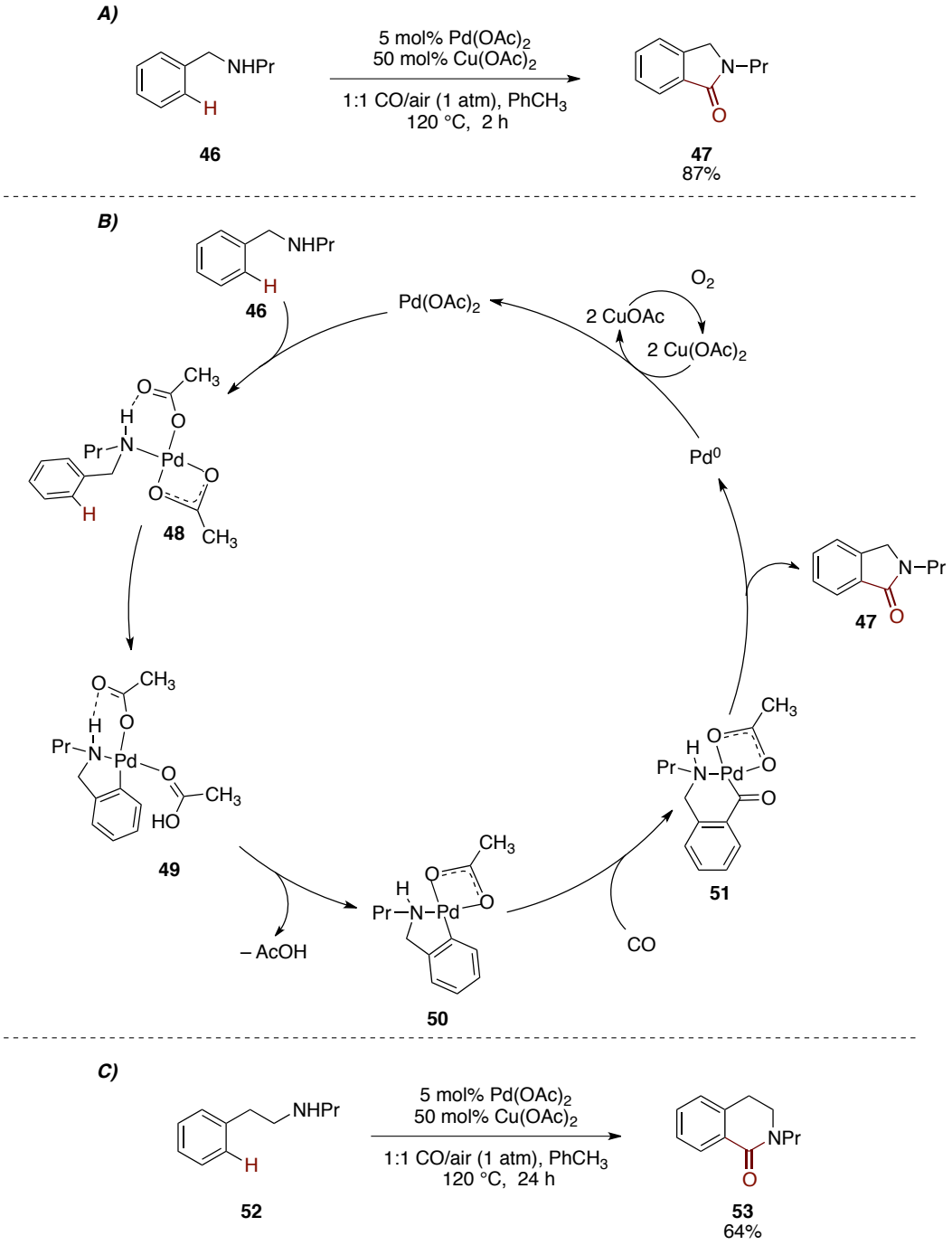


Scheme 16: Tsuji's stoichiometric, stepwise C(sp^2)–H carbonylation of azobenzene.

Despite this early discovery by Tsuji, it took several decades for this directing group strategy to be applied to palladium-catalysed C–H carbonylation reactions. This directing group strategy, however, would ultimately prove to be highly influential.

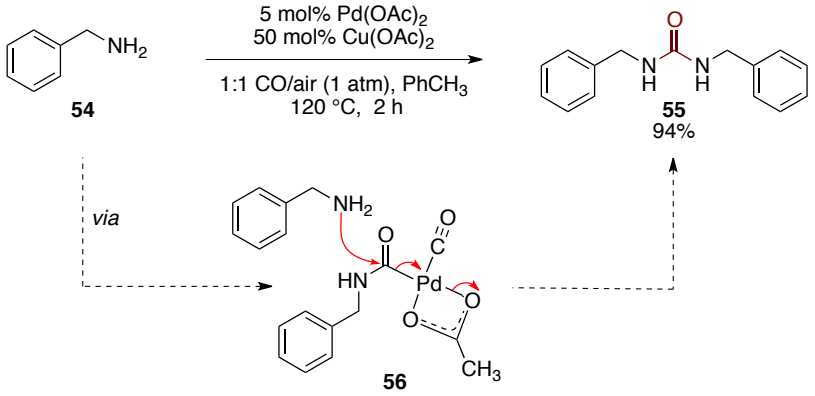
1.5.1A C(sp^2)–H carbonylation of amines, anilines and derivatives

In 2004, almost forty years after Tsuji's seminal report, Orito introduced the first example of a palladium-catalysed C–H carbonylation facilitated by a directing group. Secondary benzylamines were shown to undergo *ortho* C–H carbonylation to provide benzolactams (Scheme 17, A).[32] It was postulated that amine **46** binds to the palladium acetate catalyst to provide monoamine complex **48**, which holds the *ortho* C–H bond of the aromatic ring proximal to the palladium centre and results in C–H activation to provide palladacycle **49** (Scheme 17, B). Indeed, the palladacycles derived from the C–H activation of benzylamines are known.[61–63] Loss of acetic acid from the palladacycle, followed by carbon monoxide insertion led to six-membered acyl palladacycle **51**, from which the benzolactam product is liberated by C–N reductive elimination. Finally, oxidation of palladium(0) regenerates the palladium(II) catalyst and closes the catalytic cycle. Phenethylamines (**52**, Scheme 17, C) were also found to undergo C–H carbonylation, although the reactions were observed to be significantly slower, presumably due to the larger kinetic barrier to six-membered palladacycle formation.



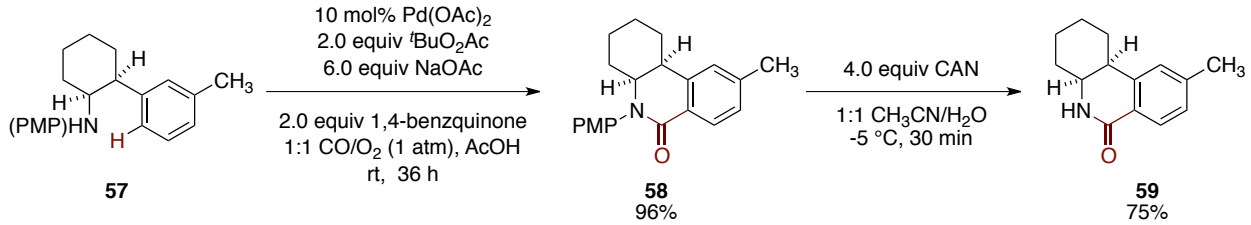
Scheme 17: Orito's C(sp^2)–H carbonylation of secondary amines. **A)** C(sp^2)–H carbonylation of benzylamines; **B)** Orito's proposed mechanism; **C)** C(sp^2)–H carbonylation of phenethylamines.

In a later paper, Orito discovered that primary amines did not undergo C–H carbonylation to provide NH-benzolactams under these reaction conditions. Instead, primary amines were observed to undergo carbonylation to provide ureas.[64] Urea formation was envisaged to proceed *via* a palladium carbamoyl complex **56** intermediate, which is then be intercepted by a second equivalent of amine to provide the urea product.[64]



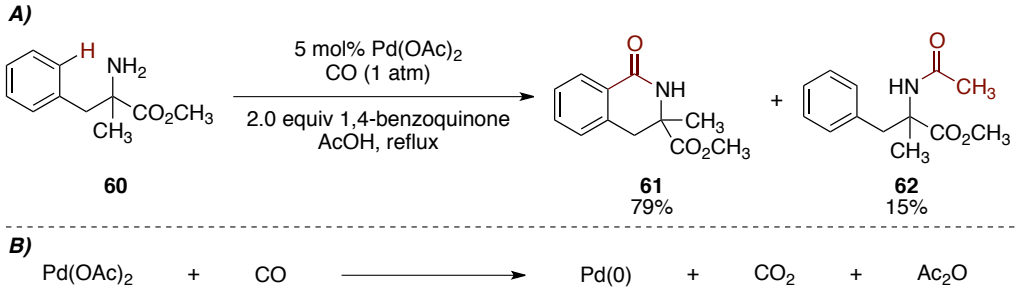
Scheme 18: Orito's carbonylation of primary amines to provide ureas.

In 2009, Gaunt detailed a solution to this problem and described a C–H carbonylation of secondary benzylamines bearing a cleavable paramethoxyphenyl (PMP) protecting group (**57**, Scheme 19).[65] Following C–H carbonylation, the PMP protecting group could be removed from the PMP protected benzolactam product (**58**) by treatment with ceric ammonium nitrate (CAN) to afford the free NH-benzolactam (**59**). Whilst this methodology enabled the synthesis of NH–benzolactams by C–H carbonylation, the steps required to install and remove the PMP protecting group represent a limitation of this methodology.



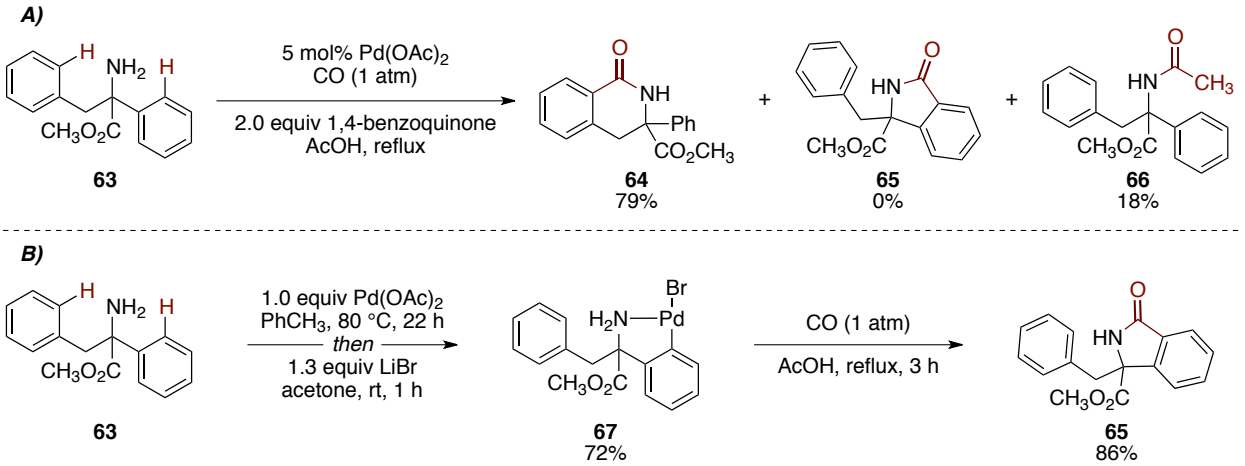
Scheme 19: Gaunt's C(sp^2)–H carbonylation of phenethylamine derivatives bearing a cleavable PMP group.

In a concurrent study, Grannel indicated that sterically encumbered primary amines bearing an α quaternary centre to the nitrogen could undergo C–H carbonylation to provide direct access to δ-NH-benzolactams without the concomitant formation of ureas (Scheme 20, A).[66] Interestingly, the C–H carbonylation of amine **60** provided δ-NH-benzolactam **61** in 79% yield, but also provided an acetamide **62** side product in 15% yield, which presumably arises from the acetylation of starting amine **60**. Moiseev has reported that palladium acetate decomposes under a carbon monoxide atmosphere to generate acetic anhydride.[44] It is possible that the acetic anhydride generated in this decomposition is intercepted by starting amine **60** to furnish acetamide **62** (Scheme 20, B).



Scheme 20: Grannel's C(sp^2)–H carbonylation of primary amines. **A)** The catalytic reaction; **B)** The reaction of palladium acetate with carbon monoxide as observed by Moiseev.

Remarkably, the catalytic C–H carbonylation of competition substrate **63** resulted in the selective formation of δ-NH-benzolactam **64**, without the formation of γ-NH-benzolactam **65** (Scheme 21, A).[66] This is perhaps an unexpected observation; one might expect **63** to undergo five-membered cyclopalladation preferentially, which, in turn would lead to γ-NH-benzolactam **65**. Indeed, the stoichiometric cyclopalladation of amine **63** was found to result in both five and six-membered palladacycles, with five-membered palladacycle **67** being the major product. Following isolation, the five-membered palladacycle **67** underwent carbonylation to exclusively provide the γ-NH-benzolactam **65** product (Scheme 21, B). To rationalise the disparity between catalytic and stoichiometric experiments, it was suggested that C–H activation was reversible under catalytic conditions and thus five and six-membered palladacycles were in equilibrium. It was supposed that the outcome of the catalytic reaction was determined by preferential reductive elimination from the larger palladacycle, resulting in exclusive δ-NH-benzolactam **64** formation under catalytic conditions.

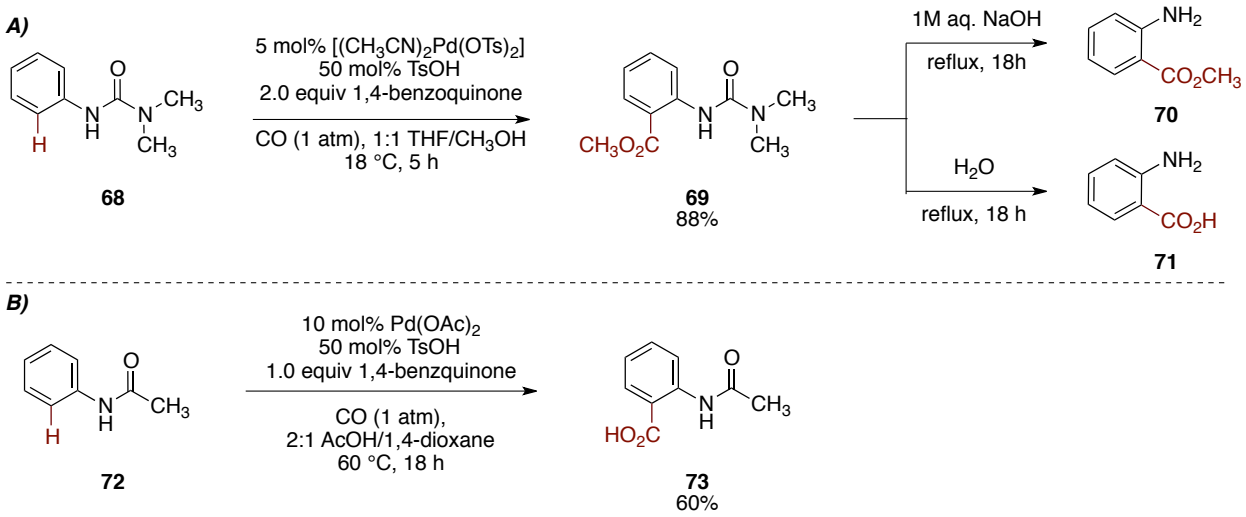


Scheme 21: Competition experiments performed by Grannel. **A)** The catalytic C–H carbonylation of a substrate with two sites of reactivity; **B)** The stoichiometric, stepwise C–H carbonylation of the same substrate.

Subsequent to Orito's initial report,[32] Lloyd-Jones and Yu investigated the C–H carbonylation of aniline derivatives. Lloyd-Jones' report utilised a urea directing group to effect *ortho* C–H carbonylation. The C–H carbonylation products were subsequently cleaved to afford either the free-NH_2 methyl anthranilate (**70**) or the anthranilic acid (**71**) product (Scheme 22, A).[67] Meanwhile, Yu's reaction employed an acetanilide-directing group to direct *ortho* C–H carbonylation, however, the removal of this directing group from the carbonylation products was not demonstrated within the paper.[43] Indeed, it is generally accepted that acetanilide-directing groups are challenging to remove,[68] meaning that Lloyd-Jones' aniline C–H carbonylation strategy is arguably of greater synthetic utility.

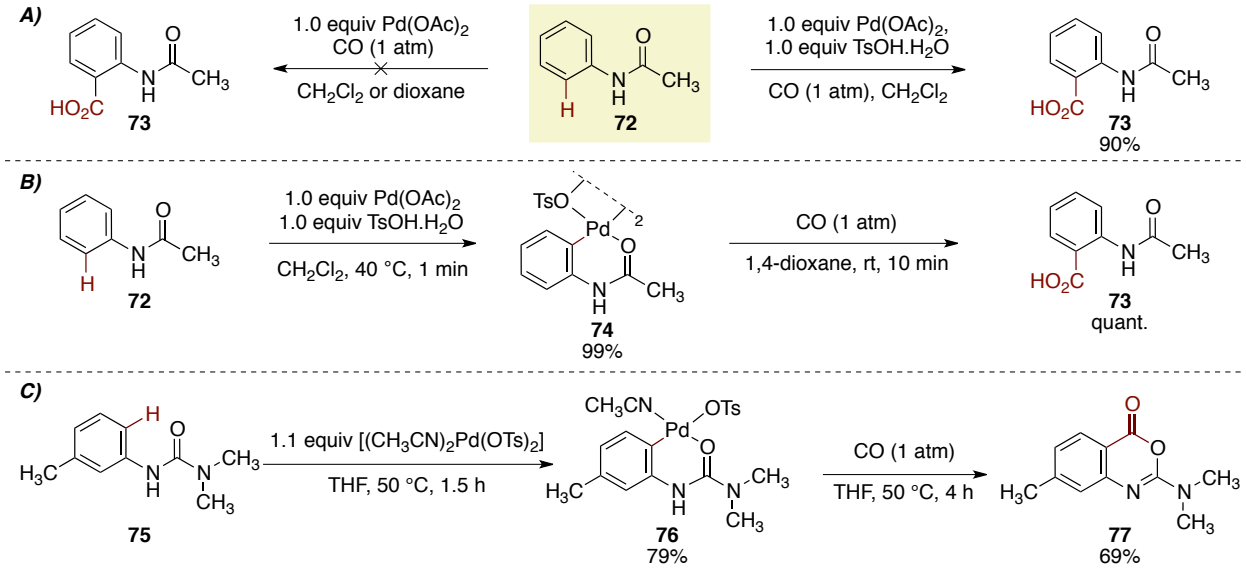
In both reactions (Scheme 22, A and B), the active catalyst is believed to be palladium(II) tosylate.[43,67] Although palladium acetate is employed in Yu's C–H carbonylation, it is known that palladium acetate can react with TsOH to generate palladium tosylate *in situ*.[69] Indeed, Yu confirmed that treatment of acetanilide **72** with palladium acetate and carbon monoxide led only to recovered starting material (Scheme 23, A, left). It was suggested by Yu that deleterious carbon monoxide mediated reduction of the palladium(II) catalyst had outcompeted C–H activation in this experiment.[43] However, Yu established that the addition of TsOH to the stoichiometric reaction of acetanilide **72** provided anthranilic acid derivative **73** in excellent yield (Scheme 23, panel A, right). It was proposed that a more electrophilic palladium

tosylate catalyst was generated under these conditions, which led to an acceleration of the S_EAr C–H activation event, such that it outcompeted carbon monoxide mediated catalyst reduction.



Scheme 22: The C(sp^2)–H carbonylation of aniline derivatives. **A)** Lloyd-Jones' C(sp^2)–H carbonylation of aryl ureas; **B)** Yu's C(sp^2)–H carbonylation of acetanilides.

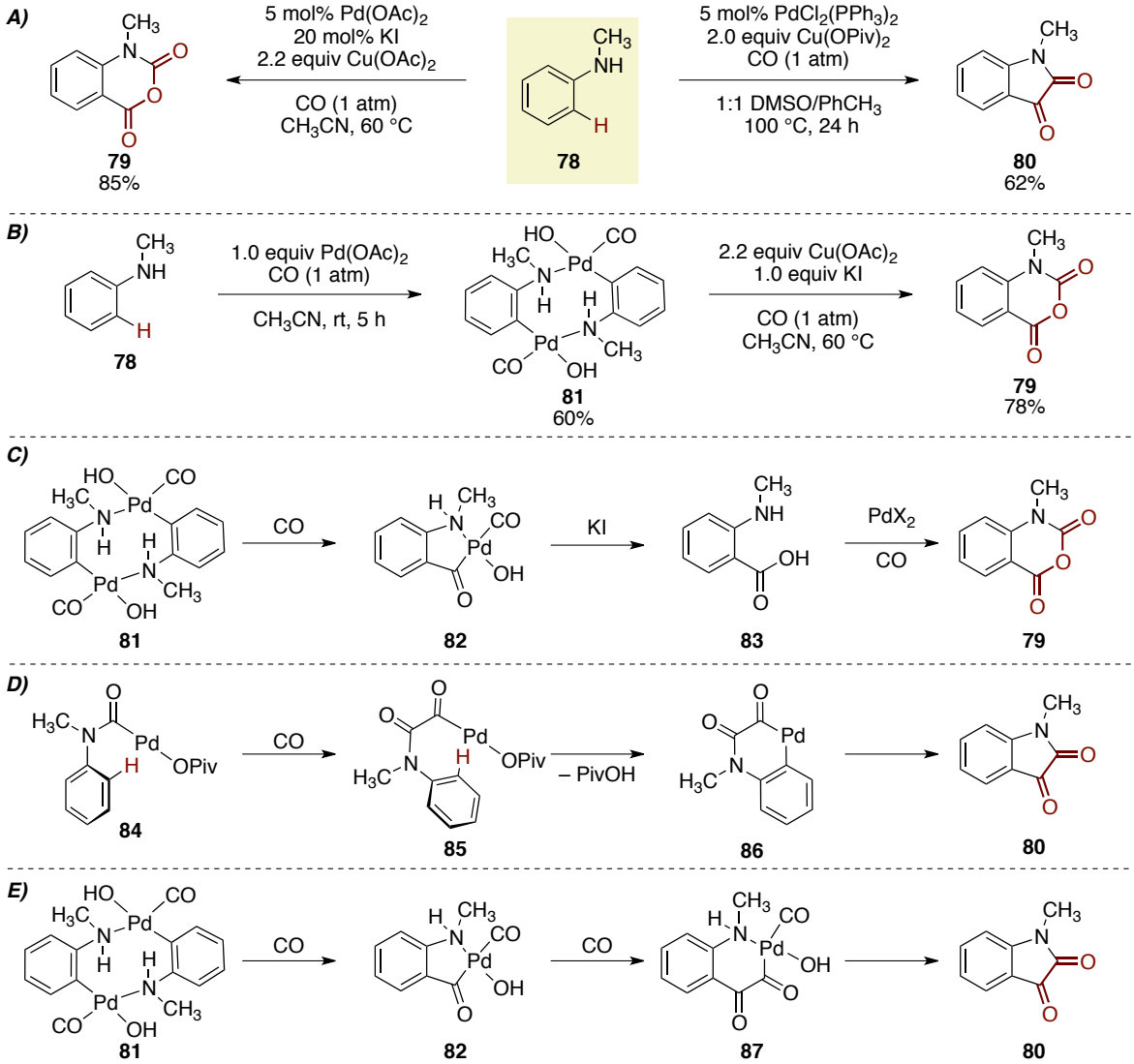
Both Yu and Lloyd-Jones demonstrated that stoichiometric C–H activation of the respective acetanilide derivatives afforded palladacycles, which could be subjected to a carbon monoxide atmosphere to provide carbonylated products (Scheme 23, panel B and C). Finally, Lloyd-Jones verified that methanolysis of cyclic imidate **77** product (Scheme 23, panel C) occurred under catalytic reaction conditions, providing the methyl anthranilate (**70**) as observed in the catalytic reaction.[67]



Scheme 23: Stoichiometric experiments to investigate the mechanism of C(sp^2)–H carbonylations of aniline derivatives. **A)** Yu's stoichiometric C(sp^2)–H carbonylation of an acetanilide in the presence (right) and absence (left) of tosic acid; **B)** Yu's stoichiometric, stepwise C(sp^2)–H carbonylation of an acetanilide; **C)** Lloyd-Jones' stoichiometric, stepwise C(sp^2)–H carbonylation of an aryl urea.

Continuing the theme of aniline directed processes, Guan[70] and Lei[71] independently conveyed distinct C–H carbonylation reactions of *N*-alkyl anilines, to afford isatoic anhydrides (**79**) and isatins (**80**) respectively (Scheme 24, A).

Guan found the stoichiometric C–H activation of *N*-methylaniline afforded dimeric palladacycle **81** under a carbon monoxide environment (Scheme 24, B). Subjecting this dimeric palladacycle to carbon monoxide in the presence of potassium iodide resulted in the formation of isatoic anhydride **79**. Interestingly, in the absence of potassium iodide, the formation of isatoic anhydride **79** was not observed, suggesting potassium iodide plays a key role in the carbonylation mechanism. Guan proposed that carbon monoxide insertion provided acyl palladium hydroxide **82**, which leads to the formation of anthranilic acid **83** (Scheme 24, C). It is known that C–O reductive elimination is challenging from palladium(II) complexes[72] and, therefore, it is possible that the role of potassium iodide is convert acyl palladium hydroxide **82** to the corresponding acyl palladium iodide complex. Subsequent C–I bond reductive elimination would afford an acyl iodide, which could undergo *in situ* hydrolysis to provide anthranilic acid **83**. Guan then suggested that a second carbonylation of anthranilic acid **83** furnishes the isatoic anhydride product **79**.



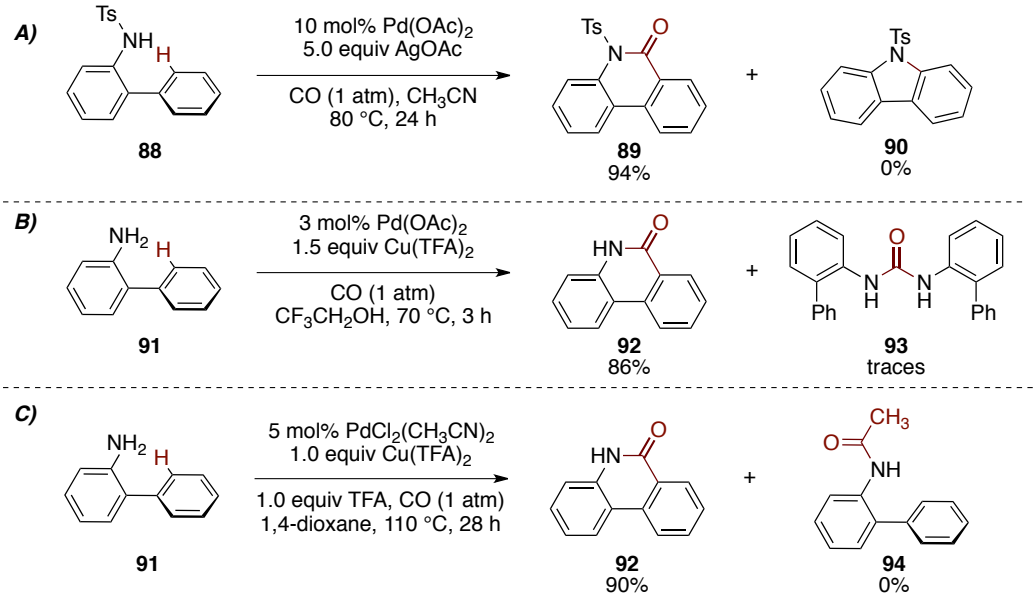
Scheme 24: The C(sp^2)–H carbonylation of *N*-alkyl anilines. **A)** Guan's C(sp^2)–H carbonylation to provide isatoic anhydride (left) and Lei's C(sp^2)–H carbonylation to provide isatins (right); **B)** Guan's stoichiometric, stepwise C(sp^2)–H carbonylation experiments; **C)** Guan's proposed mechanism for carbonylation, leading to isatoic anhydrides; **D)** Lei's proposed mechanism for isatin synthesis; **E)** An alternative proposed mechanism for Lei's isatin synthesis.

Interestingly, Lei's C(sp^2)–H carbonylation to provide isatins (Scheme 24, A, right) is conducted under similar reaction conditions to Guan's reaction (Scheme 24, A, left), but a very different mechanism was

invoked (Scheme 24, D).[71] Lei believed that C(sp^2)–H activation occurs from oxayl amide complex **85** and leads to a six-membered palladacycle **86**, which, in turn, undergoes C–C bond reductive elimination to furnish the isatin product **80**. Whilst DFT studies demonstrated the feasibility of Lei's suggested reaction pathway, the mechanism appears to be inconsistent with Guan's stoichiometric observations (Scheme 24, B). An alternative mechanism for Lei's carbonylation could involve carbon monoxide insertion into the Pd–C bond of Guan's postulated intermediate **82** (Scheme 24, E), which would afford six-membered palladacycle **87**, from which C–C bond reductive elimination would provide isatin **80**.

More recently, there have been a number of reports on the palladium-catalysed C(sp^2)–H carbonylation of 2-arylanilines and its derivatives (Scheme 25). In the first of these publications, Chuang disclosed the C(sp^2)– H carbonylation of *N*-tosyl 2-aryl anilines (Scheme 25, A).[73] Initial conditions for this C–H carbonylation, in dimethylsulfoxide (DMSO), resulted in the concomitant formation of a carbazole side product **90**. Presumably, C–H activation of **88** affords a palladacycle, from which C–N reductive elimination competes with carbon monoxide insertion. Chuang discovered that the formation of carbazole **90** could be avoided if the reaction was conducted in an acetonitrile solvent, allowing δ-lactam **89** to be formed as the exclusive product.

At a similar time, Zhang described the C–H carbonylation of 2-aryl anilines (Scheme 25, B).[74] In addition to the formation of δ-lactam **92**, concomitant formation of urea **93** was observed, which is comparable to Orito's previous observations on the carbonylation of primary amines.[64] Judicious choice of oxidant was found to limit the formation of the urea side product, however, its formation could not be entirely circumvented.



Scheme 25: C(sp^2)–H carbonylations of 2-arylanilines. **A)** Chaung's C(sp^2)–H carbnylation of *N*-tosyl derivatives; **B)** Zhang's C(sp^2)–H carbonylation of 2-arylanilines; **C)** Zhu's C(sp^2)–H carbonylation of 2-arylanilines.

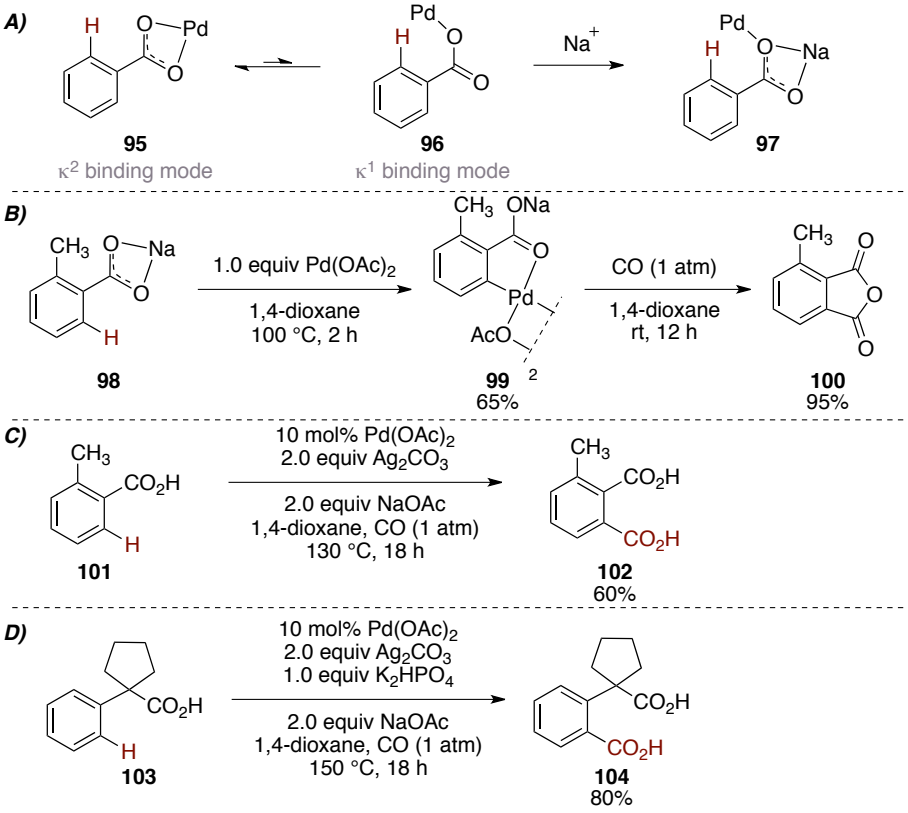
Finally, a concurrent report by Zhu also described a C–H carbonylation reaction of 2-aryl anilines (Scheme 25, C).[75] In Zhu's initial studies, significant quantities of acetamide **94** were observed when the C–H carbonylation of 2-aryl aniline **91** was performed using $Pd(OAc)_2$, CuO and carbon monoxide in acetic acid. However, Zhu demonstrated that the formation of the acetamide side product could be

precluded by reaction conditions that did not contain sources of acetate. Acetamide formation had similarly been an issue in Grannel's C–H activation of hindered, primary homobenzylic amines.[66]

To summarise, palladium-catalysed C(sp^2)–H carbonylation directed by amine and aniline functionality can be hampered by undesired side reactions, which furnish ureas[64,74] and acetamides.[66,75] Additionally, experimental evidence has suggested that C–H activation can occasionally be outcompeted by carbon monoxide mediated catalyst reduction.[43] In this scenario, it has been speculated that the C–H activation event must be accelerated such that C–H activation is preferred over catalyst reduction.[43] To this end, Lloyd-Jones and Yu have demonstrated that palladium tosylate catalysts can enable C–H carbonylation reactions, where traditional palladium acetate catalysts are unsuccessful.[43,67]

1.5.1B C(sp^2)–H carbonylation of carboxylic, phosphonic and phosphinic acids

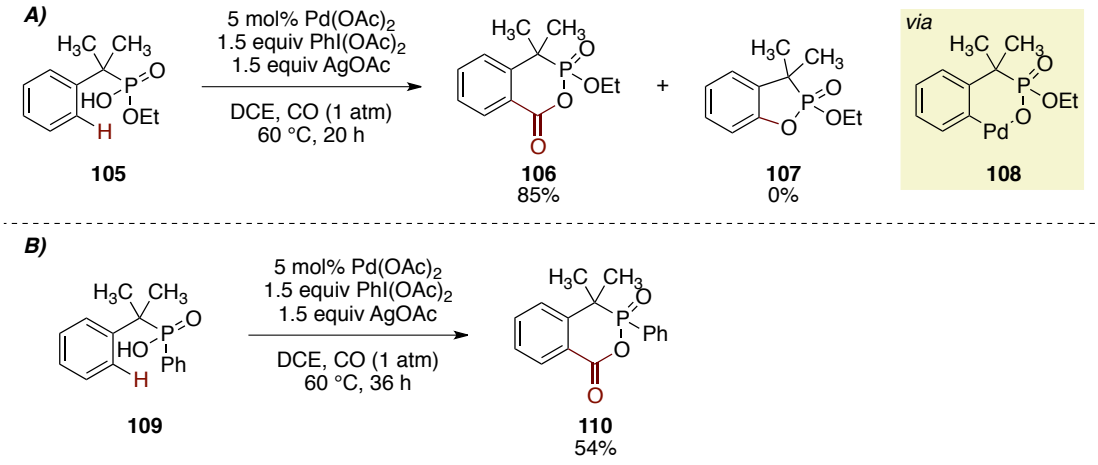
In 2008, another early demonstration of directing group enabled C–H carbonylation was reported by Yu.[76] The group's early attempts at carboxylic acid directed C–H functionalisation were unsuccessful[77] and it was suspected that an undesired coordination between the palladium and carboxylate was responsible for the lack of reactivity (Scheme 26, A). It was proposed that palladium preferentially bound the carboxylate substrates in a κ^2 fashion, which held the *ortho* C–H away from the palladium centre and prevented C–H activation (**95**, Scheme 26, A). However, it was recognised that the disfavoured κ^1 binding mode of the carboxylate would hold the palladium proximal to the *ortho* C–H bond and potentially allow C–H activation (**96**, Scheme 26, A). It was hypothesised that the introduction of a sodium countercation would bind the carboxylate in a κ^2 fashion, allowing palladium to achieve the κ^1 binding mode believed to be required for C–H activation (**97**, Scheme 26, A).



Scheme 26: Yu's C(sp^2)–H carbonylation of carboxylic acids. **A)** Binding modes of carboxylates to palladium; **B)** Stoichiometric, stepwise C(sp^2)–H carbonylation of a sodium benzoate; **C)** Catalytic C(sp^2)–H carbonylation of benzoates; **D)** C(sp^2)–H carbonylation of phenylacetic acids.

The Yu laboratory went on to show that sodium benzoate **98** underwent *ortho* C–H activation with stoichiometric palladium acetate to provide access to a five-membered palladacycle **99** in 65% yield (Scheme 26, B). This palladacycle was then subjected to a carbon monoxide atmosphere to afford phthalic anhydride **100** in 95% yield. Catalytic conditions for this transformation were developed, in which the phthalic anhydride intermediate (**100**) underwent *in situ* hydrolysis to afford phthalic acid (**101**, Scheme 26, C). Yu's C–H carbonylation reaction was then extended to phenylacetic acids (Scheme 26, D). However, it was found that α,α-disubstitution was required for the C–H carbonylation reaction to proceed. Substrates with lesser degrees of substitution on this α centre are not competent substrates for this C–H carbonylation, presumably due to the absence of a favourable Thorpe Ingold effect.[78]

A related phosphonic acid directed C–H carbonylation reaction was later described by Lee (Scheme 27, A).[79] Lee's C–H carbonylation reaction provides cyclic phosphonate products (**106**), which are a class of β-lactamase inhibitors.[80] In Lee's initial reaction optimisation studies, **107** was observed as a significant side product, which presumably derives from C–O bond reductive elimination from palladacycle **108** before carbon monoxide insertion can occur. This C–O bond reductive elimination is presumably promoted by the action of phenyliodonium diacetate, which is capable of oxidising palladium(II) to palladium(IV), wherein C–O bond reductive elimination becomes more facile.[81] Silver acetate was found to suppress the formation of this side product and exclusive formation of the carbonylated product **106** resulted. Finally, Lee extended the C–H carbonylation protocol to include phosphinic acid substrates, although longer reaction times were required in order to achieve comparable yields (Scheme 27, B).

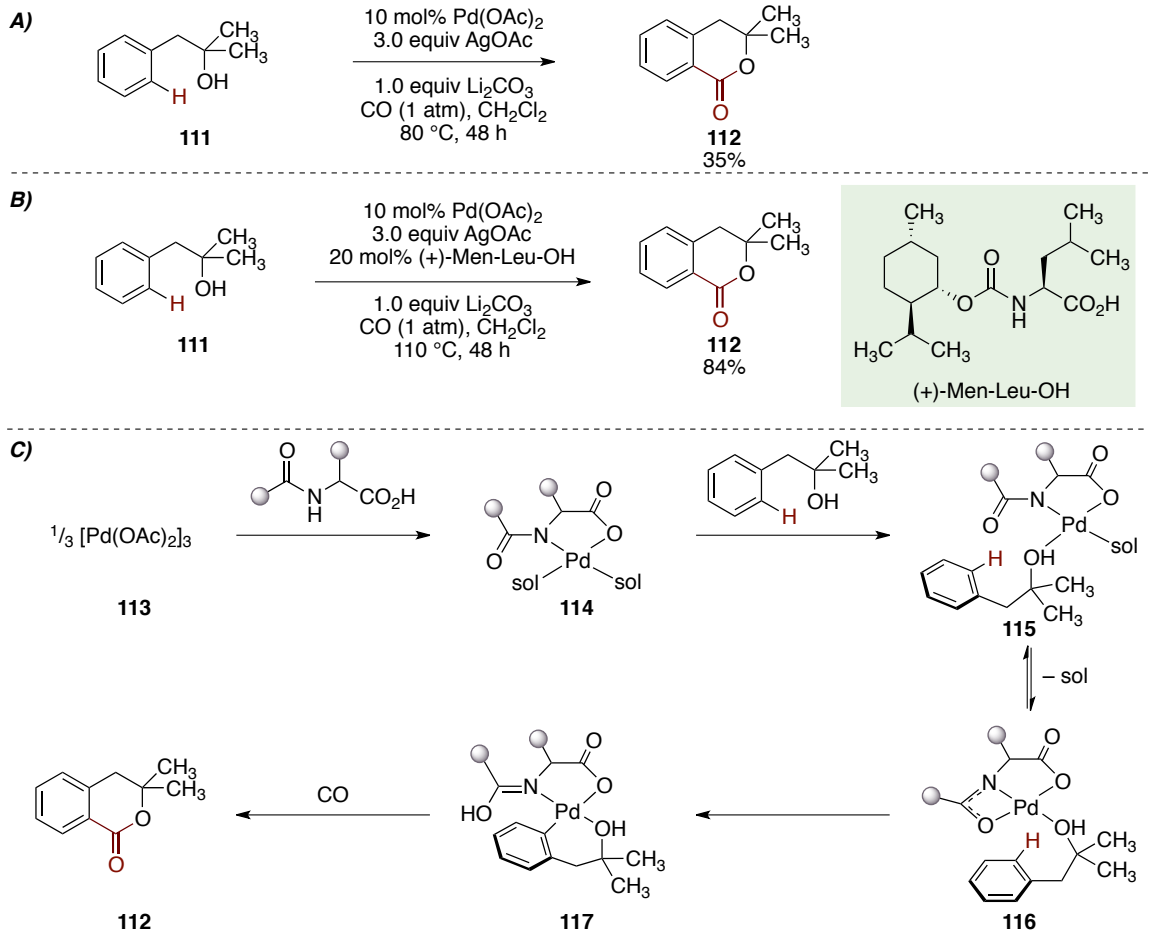


Scheme 27: Lee's C(sp^2)–H carbonylation of: **A)** phosphonic acids; **B)** phosphinic acids.

1.5.1C C(sp^2)–H carbonylation of alcohols, phenols and derivatives

Despite significant advances within the field of C–H functionalisation chemistry, palladium-catalysed C–H functionalisation reactions directed by alcohols remain rare. Alcohols are known to be weak ligands for palladium[82] and are generally considered to be poor directing groups for palladium-mediated C–H activation reactions. In addition to this, palladium(II) salts are known to oxidise primary and secondary alcohols and decompose tertiary alcohols.[83] In spite of these challenges, the Yu lab successfully developed an impressive C–H carbonylation of tertiary phenethylalcohols to provide 1-isochromanones (Scheme 28, A).[82]

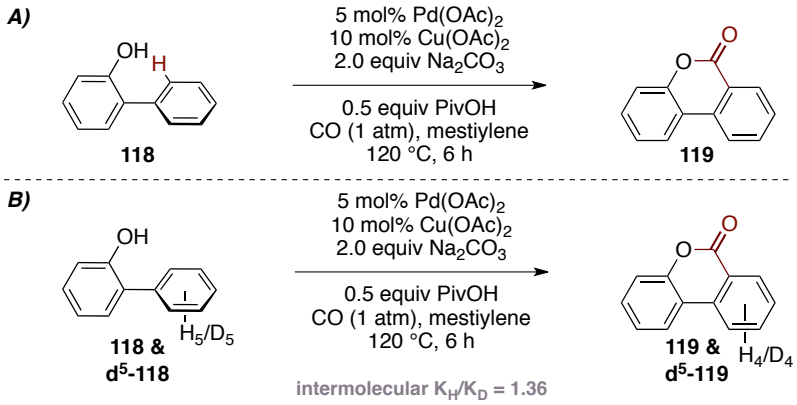
After an initial and extensive reaction optimisation, a disappointing 35% conversion of alcohol **111** was achieved. Carbon monoxide mediated catalyst decomposition was proposed as a significant issue in the reaction.[82] Accordingly, the Yu laboratory sought to accelerate the C–H activation event, such that the C–H carbonylation reaction was faster than catalyst decomposition. The group's previous research had demonstrated that *N*-acyl amino acid ligands could accelerate the C–H activation step of C–H functionalisation reactions.[84] Accordingly, a range of *N*-acyl amino acid ligands were screened in the C–H carbonylation reaction, with 20 mol% (+)-Men-Leu-OH providing the best results (Scheme 28, B). The role of the *N*-acyl amino acid ligands in the mechanism of a related C–H functionalisation reaction was later investigated by DFT calculations.[85] This study showed that *N*-acyl amino acid ligands react with trimeric palladium acetate to afford a monomeric palladium complex with two co-ordination sites occupied by solvent molecules (**114**, Scheme 28, C).[85] By adapting the mechanism determined within this study to Yu's C–H carbonylation of phenethylalcohols, it is posed that facile displacement of solvent by the alcohol provides palladium complex **115** (Scheme 28, C). C–H activation then occurs by a CMD mechanism, with the electron rich κ^2 amido ligand acting as an internal base. 1,1-Migratory insertion of carbon monoxide into the Pd–C bond of palladacycle **117**, followed by reductive elimination then provides 1-isochromanone **112**.



Scheme 28: Yu's C(sp^2)–H carbonylation of phenethylalcohols. **A)** Initial conditions for the catalytic reaction; **B)** Optimised conditions for the catalytic reaction, using an *N*-acyl amino acid ligand; **C)** Proposed role of the *N*-acyl amino acid ligands, which has been supported by DFT calculations.

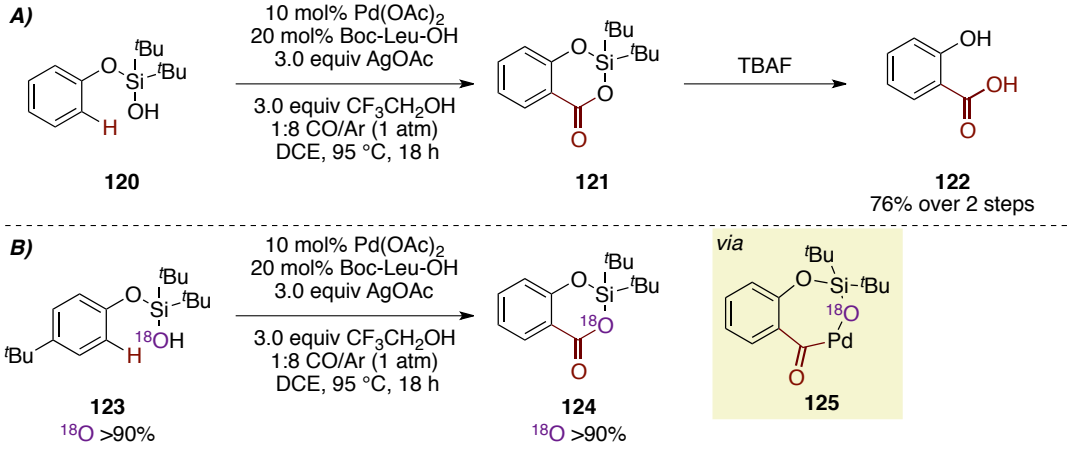
Following Yu's C(sp^2)–H carbonylation of alcohols, Shi demonstrated that the C–H carbonylation of 2-arylphenols could be used to prepare dibenzopyranones (Scheme 29, A).[86] The reaction was imagined to

proceed *via* coordination of the 2-arylphenol substrate to the palladium catalyst to furnish a palladium phenoxide complex, from which C–H activation leads to a six-membered palladacycle. Indeed, a closely related palladacycle has been characterised using x-ray crystallography by Liu.[87] Subsequent 1,1-migratory insertion of carbon monoxide into the Pd–C bond of the palladacycle was suggested to provide a seven-membered acyl palladacycle, from which C–O reductive elimination furnished the dibenzopyranone product. Shi measured the KIE value (K_H/K_D) from parallel C–H carbonylations of **118** and **d^5-118** to be 1.36 (Scheme 29 C). The magnitude of this KIE value suggests a secondary kinetic isotope effect[88] and indicates that C–H bond cleavage does not occur during the turnover-limiting step of the reaction.[89] This would be consistent with an S_EAr mechanism for C–H activation.



Scheme 29: Shi's C(sp^2)–H carbonylation of 2-arylphenols. **A)** The catalytic reaction; **B)** KIE studies.

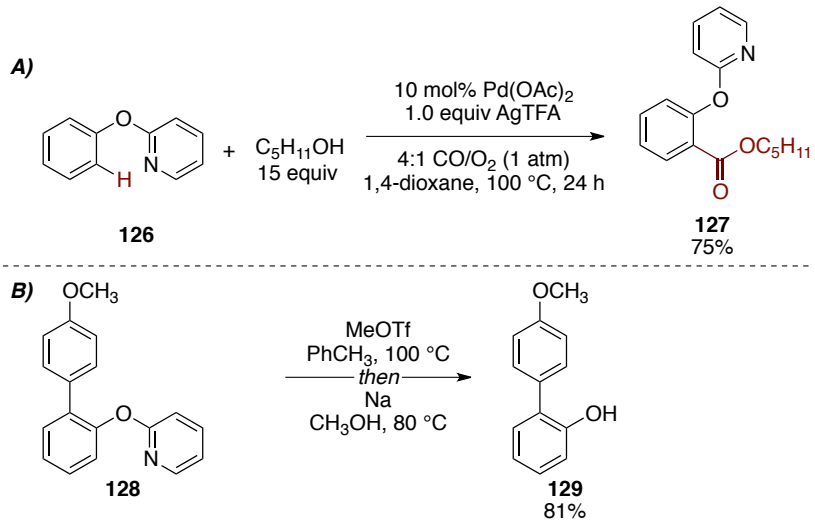
Subsequent to Shi's report, Gevorgyan developed an *ortho* C–H carbonylation of the phenol ring itself to provide direct access to salicylic acids.[90] Previous work within the group had outlined a traceless silanol directing group strategy for the *ortho* C–H alkenylation of phenol derivatives.[91] Accordingly, subjecting silanol **120** to C–H carbonylation conditions was found to provide silyl protected salicylic acid derivative **121**, which after desilylation with tetrabutylammonium fluoride (TBAF) afforded the free salicylic acid **122** (Scheme 30, A). The mechanism of the reaction was proposed to occur by a traditional C–H carbonylation manifold, comprising of C–H activation, 1,1-migratory insertion of carbon monoxide and finally reductive elimination. ^{18}O-Labelling experiments supported this mechanism and showed that the carboxylic acid oxygen is derived from the silanol-directing group (Scheme 30, B), which suggests that **125** is an intermediate in the catalytic cycle.



Scheme 30: Gevorgyan's C(sp^2)–H carbonylation of silanol derivatives of phenol. **A)** The catalytic reaction; **B)** ^{18}O-labelling studies.

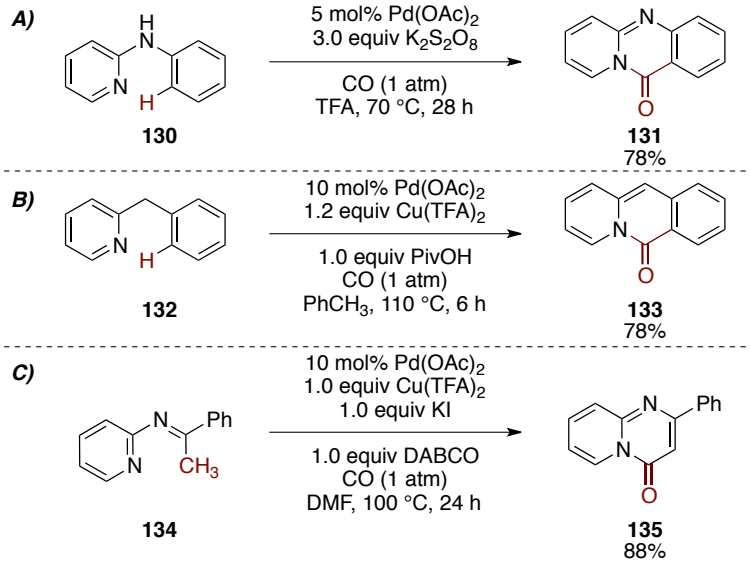
1.5.1D C(sp^2)–H carbonylation of pyridines

In 2014, an *ortho* C–H carbonylation strategy of phenol derivatives was developed by Shi, which employed a 2-pyridyl auxiliary (Scheme 31, A).[92] The removal of the 2-pyridyl directing group auxiliary from the carbonylated products was not shown by Shi, however, Ackermann has previously effected its two-step removal on related C–H arylation products (Scheme 31, B).[93] The reaction conditions required to remove the 2-pyridyl auxiliary are significantly harsher than those required in Gevorgyan's silanol auxiliary strategy and thus Shi's methodology is arguably less synthetically useful. Despite this limitation, Shi's report demonstrated for the first time that heteroaromatics could direct palladium-catalysed C–H carbonylation.



Scheme 31: Shi's 2-pyridyl directed C(sp^2)–H carbonylation of phenol derivatives. **A)** The catalytic reaction; **B)** Ackermann's removal of the 2-pyridyl auxiliary from a phenol derivative.

Following Shi's publication, a number of related reports on pyridine directed C–H carbonylation reactions were made. Zhu employed a pyridine auxiliary to direct the C–H carbonylation of aniline derivatives (Scheme 32, A).[94] Interestingly, the pyridyl motif in Zhu's C–H carbonylation acts as both a directing group and a nucleophile.

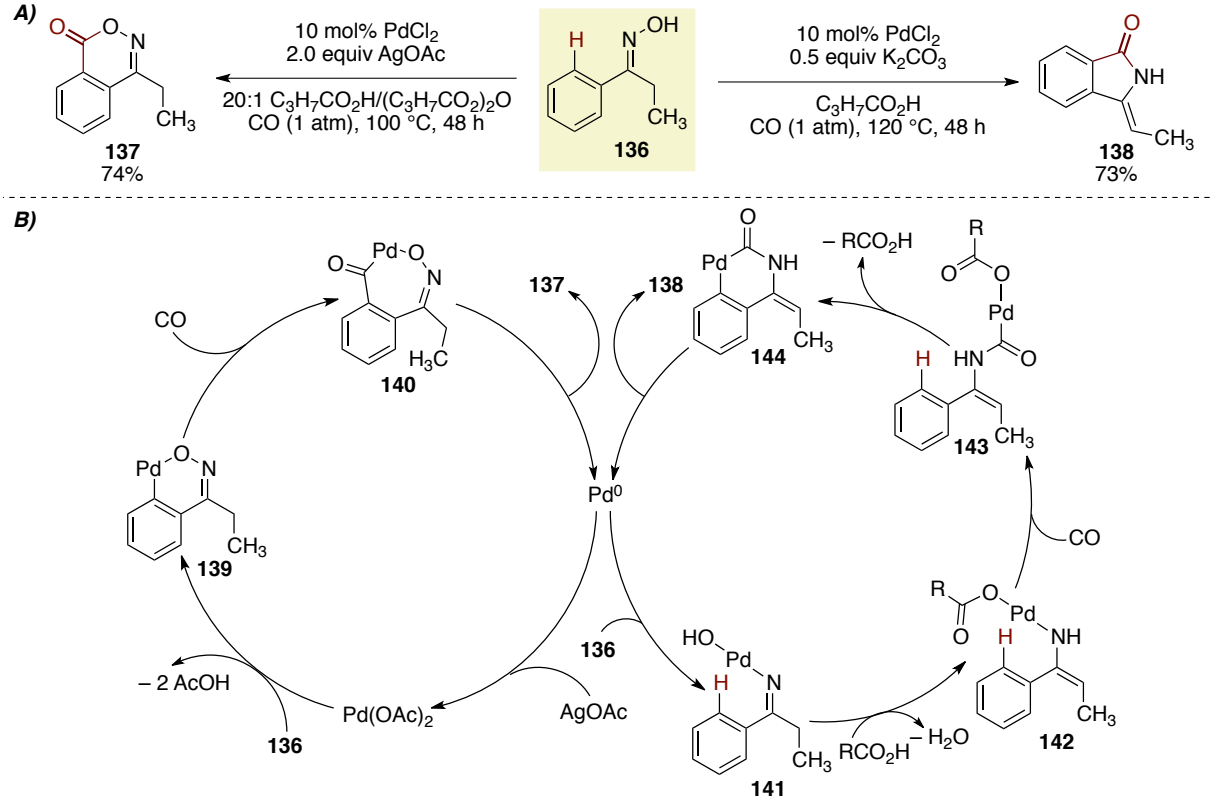


Scheme 32: Pyridine directed C(sp^2)–H carbonylations; **A)** Zhu's C(sp2)–H carbonylation of aniline derivatives; **B)** Zhu's C(sp^2)–H carbonylation of 2-benzylpyridines; **C)** Zeng's C(sp^2)–H carbonylation of enamines.

In a subsequent paper, Zhu discerned that the aniline linker was not required in this reaction and that 2-benzylpyridines could also undergo C–H carbonylation to provide pyridoquinolones (Scheme 32, B).[95] Finally, Zeng revealed that the pyridyl motif could be used to direct the C–H carbonylation of imines, which was postulated to occur *via* the enamine tautomer (Scheme 32, C).[96] All of these pyridine-directed C–H carbonylation reactions were anticipated to follow a traditional C–H carbonylation mechanism, comprising of steps of C–H activation, 1,1-migratory carbon monoxide insertion and reductive elimination.

1.5.1E C(sp^2)–H carbonylation of oximes

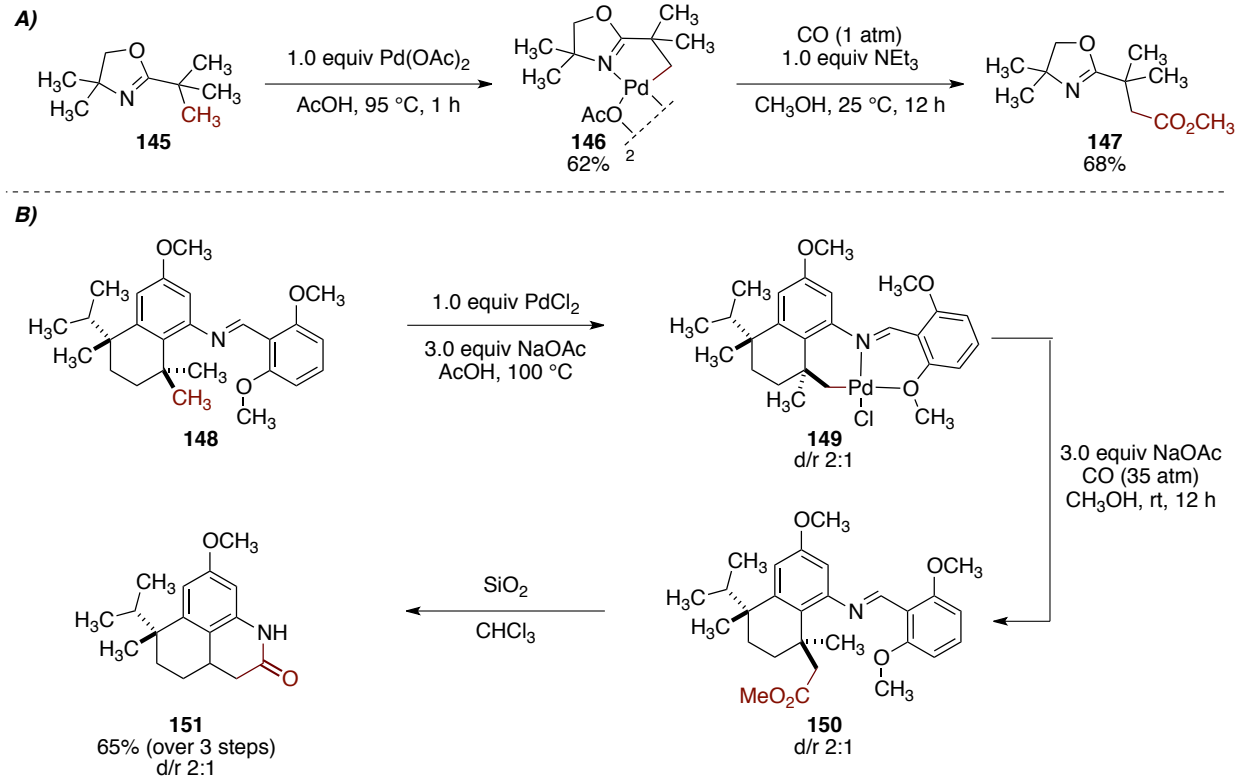
In 2015, Jiang disclosed a divergent oxime directed C–H carbonylation strategy, in which distinct reaction conditions could be exploited to form different products.[97] In the presence of silver acetate, the C–H carbonylation of oximes (**136**) affords benzo-oxazinones (**137** Scheme 33, A, left). However, in the absence of silver acetate, the reaction furnishes isoindolinones (**138**, Scheme 33, A, right). In the presence of silver acetate, it was suspected that oxime directed C–H activation affords palladacycle **139**, from which 1,1-migratory carbon monoxide insertion and reductive elimination furnishes the benzo-oxazinone **137** product (Scheme 33, B, left). The resulting palladium(0) complex is then oxidised by silver acetate to regenerate the palladium(II) catalyst. In the absence of silver acetate however, palladium(0) is understood to oxidatively insert into the N–O bond of the oxime,[98] providing access to complex **141** (Scheme 33, B, right). Ligand exchange followed by 1,1-migratory carbon monoxide insertion leads to carbamoyl palladium **143**. C–H activation of this intermediate to provide palladacycle **144** and a subsequent reductive elimination step gave isoindolinone **138** and the regenerated palladium(0) catalyst. An alternative mechanism for this reaction could involve C–H activation of complex **142**, which would provide a five-membered palladacycle (not drawn), from which 1,1-migratory insertion of carbon monoxide would afford carbamoyl palladacycle **144**.



Scheme 33: Jiang's divergent C(sp^2)–H carbonylation of oximes. **A)** The catalytic reactions in the presence (left) and absence (right) of AgOAc; **B)** Jiang's proposed mechanisms for the reactions.

1.5.2 C(sp^3)–H carbonylation reactions

Despite the wealth of palladium-catalysed C(sp^2)–H carbonylation chemistry, analogous C(sp^3)–H carbonylation reactions are less well developed. The scarcity of C(sp^3)–H carbonylation reactions is, arguably, reflective of the relative difficulty in activating C(sp^3)–H bonds.[99] In 1990, Balavoine and Clinet described the first example of a stoichiometric C(sp^3)–H carbonylation, in which palladacycle **146** was formed by treating dihydrooxazole **145** with stoichiometric palladium acetate.[100] Subjection of a methanolic solution of palladacycle **146** to a carbon monoxide atmosphere resulted in the formation of methyl ester **147**. In 2002, Sames applied this stoichiometric C–H carbonylation methodology to access an advanced intermediate in the synthesis of teleocidin B4.[101] Reacting imine **148** with palladium chloride resulted in C(sp^3)–H activation to provide six-membered palladacycle **149**. Carbonylation of this palladacycle in a methanol solvent provided methyl ester **150**, which was immediately treated with SiO_2 to effect imine hydrolysis and lactamisation to furnish lactam **151**. These early stoichiometric examples provided important precedents for C(sp^3)–H carbonylation and possibly inspired the development of catalytic processes.

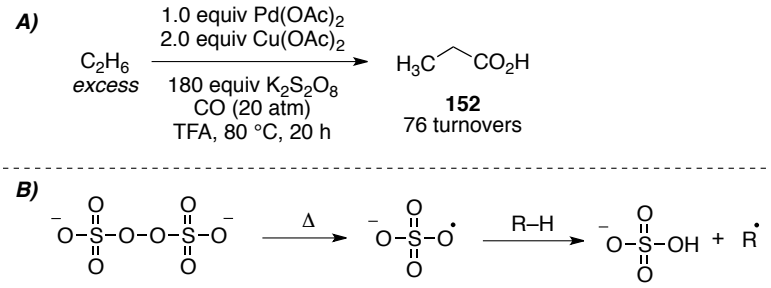


Scheme 34: Early stoichiometric, stepwise examples of C(sp^3)–H carbonylation. **A)** Balavoine and Clinet's stepwise C(sp^3)–H carbonylation of a dihydrooxazole; **B)** Sames' stepwise C(sp^3)–H carbonylation towards the synthesis of telecidin B4.

1.5.2A Radical mediated C(sp^3)–H carbonylation

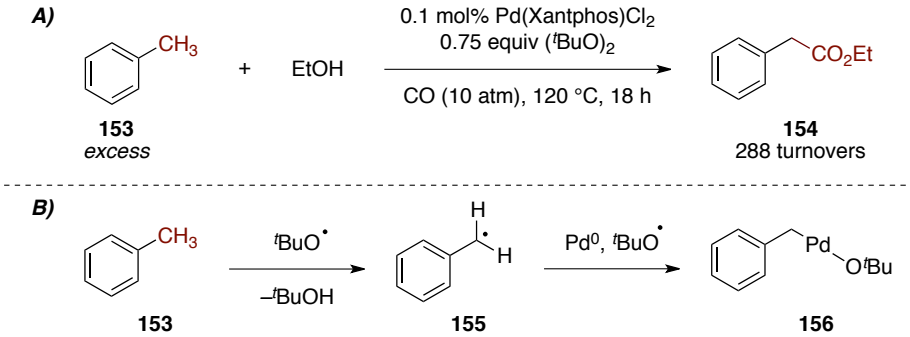
In 1994, Fujiwara published the first example of a catalytic C(sp^3)–H carbonylation reaction, which converted methane and ethane to their corresponding carboxylic acids (Scheme 35, A).[102] In this reaction, it is probable that the C–H activation event proceeds *via* a radical pathway; $K_2S_2O_8$ is known to undergo homolytic cleavage to provide radicals that can abstract hydrogen atoms from alkanes (Scheme 35, B).[103] The resulting carbon-based radicals can then interact with the palladium catalyst and, ultimately, form carboxylic acids. Unfortunately, the requirement of both high pressures (30 atm) and

excess alkane substrate severely limit the synthetic utility of this transformation. Nonetheless, this work remains an important first example of palladium-catalysed C(sp^3)–H carbonylation.



Scheme 35: Fujiwara's catalytic C(sp^3)–H carbonylation of alkanes. **A)** The catalytic reaction; **B)** Generation of carbon-based radicals from the homolytic cleavage of persulfate.

Two decades later, Huang built upon Fujiwara's seminal studies and successfully harnessed radical chemistry to affect the C(sp^3)–H carbonylation at benzylic positions (Scheme 36, A).[104] Unfortunately, an excess of substrate was still required in the methodology, which similarly restricted its synthetic utility. The reaction was hypothesised to proceed *via* the homolytic cleavage of di-*tert*-butyl peroxide to afford the ^{t}BuO$^\bullet$ radical, which abstracts a benzylic hydrogen to afford benzyl radical **155** (Scheme 36, B). The resultant benzylic radical **155** and a second ^{t}BuO$^\bullet$ radical can then add to palladium(0) to afford a palladium(II) complex **156**. Alkoxide ligand exchange, followed by carbon monoxide insertion and a final C–O bond reductive elimination was suggested to provide the phenylacetic ester products.



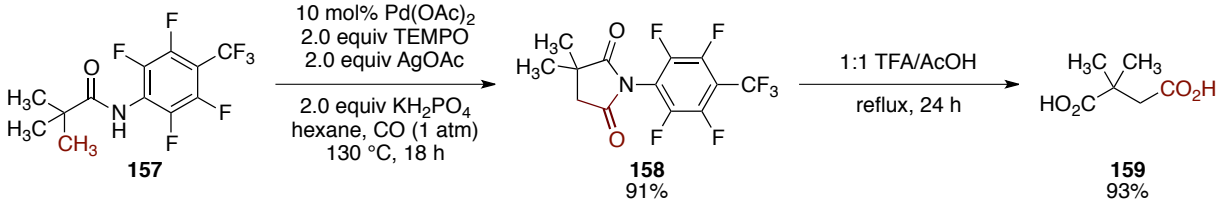
Scheme 36: Huang's catalytic C(sp^3)–H carbonylation of benzylic positions. **A)** The catalytic reaction; **B)** Huang's proposed mechanism.

1.5.2B Directing group auxiliary mediated C(sp^3)–H carbonylation

Directing group auxiliaries provide a reliable means of effecting C(sp^3)–H activation[99] and have thus been extensively applied in palladium-catalysed C(sp^3)–H carbonylation reactions.[105–109] Despite the success of this strategy, the additional synthetic steps required to install and remove the auxiliaries is a significant disadvantage of the approach. In particular, removal of the auxiliary from the carbonylated products can require harsh reaction conditions, which means sensitive functional groups are often not tolerated.[110]

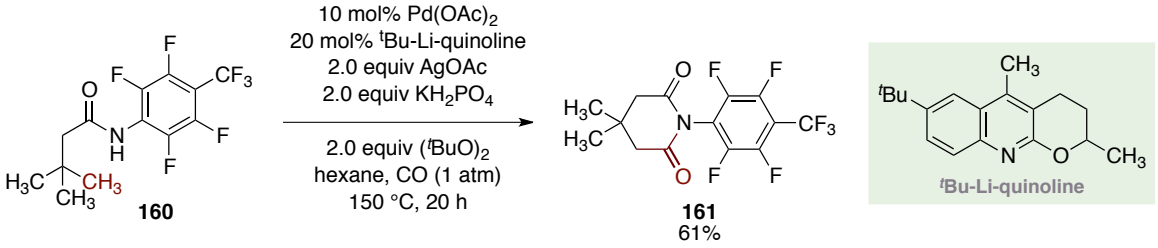
In 2010, Yu reported the first example of a catalytic C(sp^3)–H carbonylation reaction directed by an auxiliary (Scheme 37).[105] A bespoke amide directing group auxiliary was found to be essential for efficient C–H carbonylation, with other directing groups such as carboxylic acids, hydroxamic acids, oxazolines and pyridines proving unreactive under these C–H carbonylation conditions. Importantly, Yu demonstrated that a quaternary carbon centre was not required in the α position of the amide. This had been a significant limitation of Yu's earlier C(sp^2)–H carbonylation of phenylacetic acids.[76] Finally, it was

demonstrated that the bespoke amide auxiliary could be cleaved, albeit under harsh conditions, to provide access to valuable 1,4-dicarbonyl products (Scheme 37).



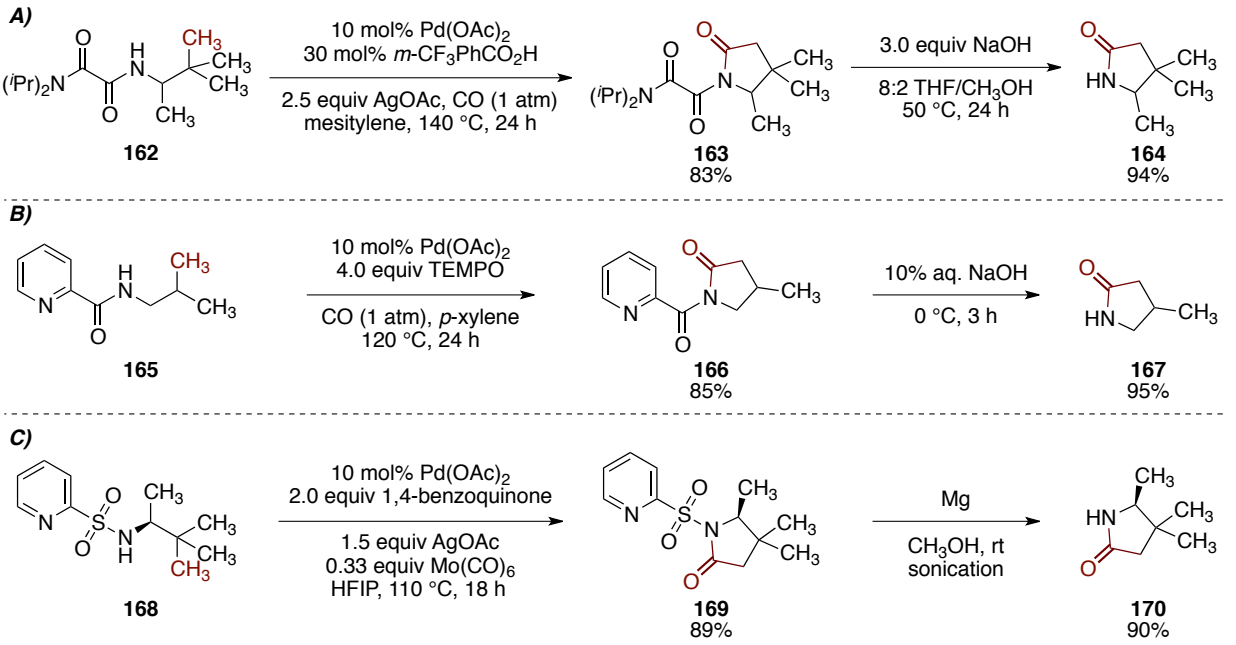
Scheme 37: Yu's C(sp^3)–H carbonylation directed by an amide auxiliary.

To extend this chemistry to the synthesis of six-membered cyclic imides, Yu developed a series of quinoline ligands to facilitate C–H functionalisation reactions *via* 6-membered palladacycles.[106] In the absence of ligands, amides such as **160** were recovered unchanged when subjected to C–H carbonylation conditions, presumably due to the difficulties associated with the six-membered cyclopalladation at C(sp^3)–H bonds.[111] However, the use of ^{t}Bu-Li-quinoline enables the C–H carbonylation of amide **160** providing access to carbonylated product **161**. The precise role of the ligand and how it alters the reactivity of palladium to enable γ C–H activation remains unclear.



Scheme 38: Yu's ligand enabled δ-C(sp^3)–H carbonylation.

Following Yu's report, a number of bidentate auxiliary-directed C(sp^3)–H carbonylation reactions were disclosed. In the first of these reports, Zhao demonstrated that oxalyl amide auxiliaries could direct the C(sp^3)–H carbonylation of derivatised amines (Scheme 39, A).[107] The oxalyl amide auxiliary could be removed from the carbonylated product under basic conditions to afford γ-lactam **164**. Subsequently, Wang employed Daugulis' picolinamide directing group auxiliary[112] to effect the C(sp^3)–H carbonylation reaction of amine derivatives (Scheme 39, B).[108] The picolinamide auxiliary could also be removed under basic conditions, but required lower reaction times and temperatures relative to the oxalyl amide auxiliary. Finally, Carretero illustrated the use of a (2-pyridyl)sulfonylamide directing group auxiliary in C(sp^3)–H carbonylation; this could be cleaved from the carbonylated products under relatively mild reaction conditions to give γ-lactam **167**. (Scheme 39, C).[109] Carretero's reaction employs molybdenum hexacarbonyl, which is known to act as a slow release source of carbon monoxide.[113] The authors hypothesised that this limits the concentration of carbon monoxide in solution, minimising reductive palladium(II) catalyst degradation.[109] All of three bidentate auxiliary directed C(sp^3)–H carbonylation reactions are proposed to occur *via* five-membered palladacycles, which are subsequently carbonylated.



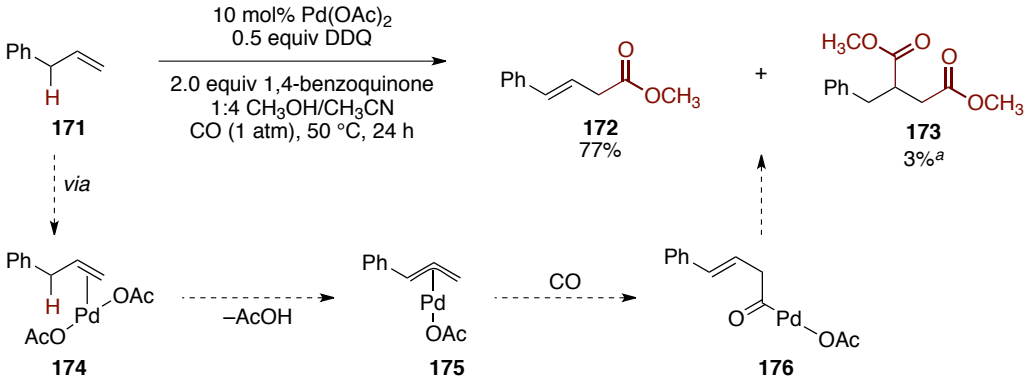
Scheme 39: Bidentate auxiliary directed C(sp^3)–H carbonylations. **A)** Zhao's oxalyl amide directed reaction; **B)** Wang's picolinamide directed reaction; **C)** Carretero's (2-pyridyl)sulfonylamide directed reaction.

1.5.2C Native directing group mediated C(sp^3)–H carbonylation

The directing group auxiliary strategy has been led to the development of a number of C–H carbonylation reactions, however the additional synthetic steps required to install and remove auxiliaries represents a significant limitation on the synthetic utility of such processes. Wary of these limitations, researchers within the field of catalytic C–H functionalisation have more recently endeavoured to move towards using functional groups that are commonly found in organic molecules in order to direct C–H activation; such groups are often referred to as 'native directing groups'. As a result of these efforts, it is now the case that the majority of reported palladium-catalysed C(sp^2)–H carbonylation reactions employ native directing groups; reactions directed by amines,[32,66] anilines,[70,71,74,75] carboxylic acids,[76] phosphonic acids,[79] alcohols,[82] phenols[86] and oximes[97] are known. Despite the success of the native directing group strategy in C(sp^2)–H carbonylation, examples of palladium-catalysed C(sp^3)–H carbonylation reactions employing native directing group strategies remain rare.

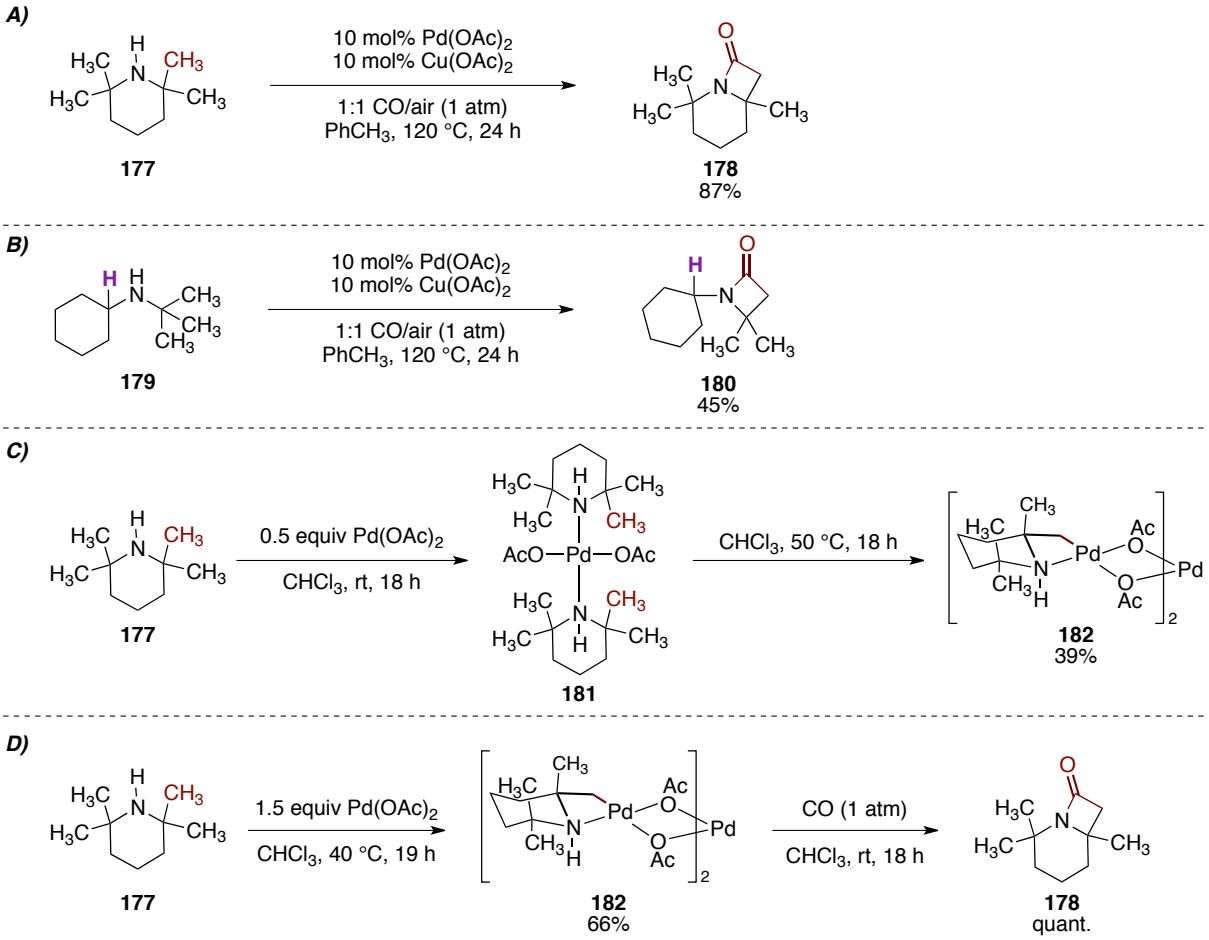
An early illustration of a C(sp^3)–H carbonylation reaction controlled by native functionality was made by Jiang, who reported a selective C(sp^3)–H carbonylation of allyl arenes (Scheme 40).[114] This work built upon the pioneering work of White, who demonstrated that palladium(II) salts can affect the allylic C–H activation of alkenes to afford π-allyl palladium complexes (**175**).[115] Although it is widely accepted that π-allyl palladium complexes result from allylic C–H activation, the precise mechanistic details of this C–H activation step remain unclear.[116] Under a carbon monoxide atmosphere, Jiang envisaged that π-allyl palladium complex **175** underwent 1,1-migratory carbon monoxide insertion to afford acyl palladium **176**, which could be intercepted by the methanol solvent to provide esters (**172**). Jiang's reaction conditions employed two oxidants, 1,4-benzoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The role of the DDQ additive appears to be to suppress the formation of doubly carbonylated product **173**, which forms in 33% yield when 2.5 equivalents of 1,4-benzoquinone are used alone. The reported scope of the reaction is limited to allyl arenes, which represents a limitation of the methodology. Nonetheless,

Jiang's allylic C(sp^3)–H carbonylation reaction is a conceptually interesting advance on the Tsuji-Trost allylation,[117] as it allows the functionalisation of allyl compounds whilst obviating the requirement of an allylic leaving group.



Scheme 40: Jiang's alkene directed C(sp^3)–H carbonylation and proposed mechanism; [a] GC yield

In 2014, Gaunt disclosed a C(sp^3)–H carbonylation of sterically hindered secondary aliphatic amines, which furnished β-lactam products (Scheme 41, A).[33] Aliphatic amines are common functionalities in pharmaceutical agents, biologically active molecules and functional materials.[118] Indeed, over 20% of the top 200 selling drugs of 2015 contained an aliphatic amine motif.[119] Due to their prevalence in biologically active compounds, aliphatic amines represent an important class of native functionality that is capable of directing palladium-catalysed C(sp^3)–H carbonylation.

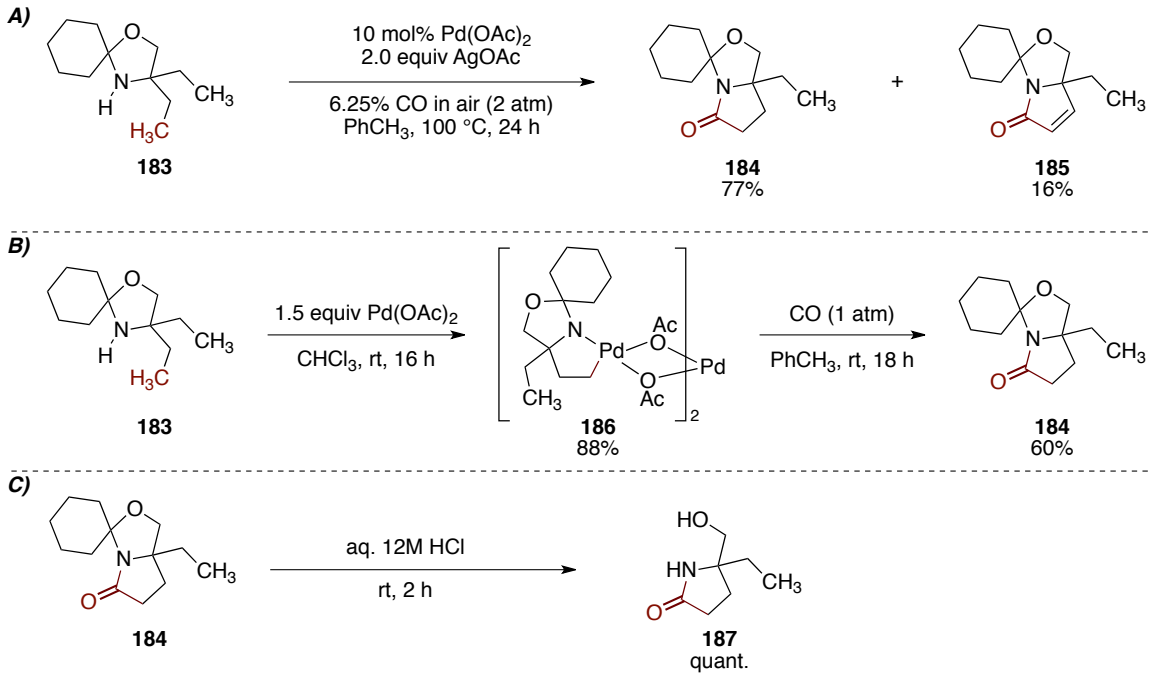


Scheme 41: Gaunt's C(sp^3)–H carbonylation of secondary aliphatic amines. **A)** The catalytic reaction; **B)** The formation of a four-membered palladacycle from a bisamine complex; **C)** The direct formation of a palladacycle and its carbonylation.

Gaunt exemplified the C(sp^3)–H carbonylation of aliphatic amines on a number of scaffolds bearing quaternary carbon centres on either side of the amine linkage.[33] A limited number of substrates bearing a tertiary carbon centre directly attached to nitrogen were also found to be amenable to C(sp^3)–H carbonylation, however these reactions were generally low yielding (Scheme 41, B). It was speculated that competitive β-hydride elimination was likely to be responsible for the poor performance of these substrates in the C(sp^3)–H carbonylation reaction.[33]

To investigate the mechanism of the carbonylation reaction, 2,2,6,6-tetramethylpiperidine **177** was subjected to 0.5 equivalents of palladium acetate, which resulted in the formation of a co-ordinatively saturated bisamine complex **181** (Scheme 41, C). Heating of bisamine complex **181** at 40 °C was believed to result in dissociation of an amine ligand, providing a monoamine complex that is amenable to C–H activation; an unusual four-membered palladacycle **182** was isolated in support of this hypothesis. Subjecting the four-membered palladacycle to a carbon monoxide atmosphere resulted in carbonylation to afford β-lactam **178** in quantitative yield (Scheme 41, D).

Gaunt went on to extend the C(sp^3)–H carbonylation reaction to include derivatives of 1,2-amino alcohols *via* five-membered ring cyclopalladation (Scheme 42, A).[120] 1,2-Amino alcohols are widely accepted to be incompatible with palladium-catalysed C–H activation due to bis-chelation of the 1,2-amino alcohol motif to palladium(II) salts.[121,122] However, protection of the 1,2-amino alcohol with a ketone provides an oxazolidine that obviates this issue. Furthermore, the highly sterically hindered nature of oxazolidine **183** precludes bisamine formation; treatment of the oxazolidine with palladium acetate at room temperature results in C–H activation, providing palladacycle **186** directly (Scheme 42, B). The palladacycle was then carbonylated under a carbon monoxide atmosphere to afford γ-lactam **184** in modest yield.

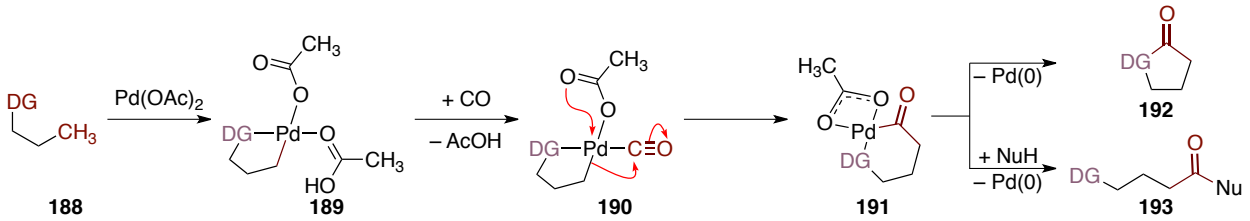


Scheme 42: Gaunt's C(sp^3)–H carbonylation of 1,2-amino alcohol derivatives. **A)** The catalytic reaction; **B)** Stoichiometric, stepwise carbonylation of oxazolidine; **C)** C(sp^2)–H carbonylation of vinyl-oxazolidine leading to the observed side product; **D)** Removal of the protecting group to afford the free carbonylated amino alcohol product.

Finally, Gaunt showed that the cyclohexyl protecting group could be removed from the carbonylated products under acidic conditions to furnish the corresponding functionalised amino alcohol **187** in quantitative yield (Scheme 42, C). Although two additional synthetic steps were required to install and remove the oxazolidine-protecting group, these manipulations were high yielding.

1.6 Summary of palladium catalysed C–H carbonylation

Extensive efforts over several decades have meant that C–H carbonylation has advanced from stoichiometric transformations of limited synthetic utility to powerful, catalytic disconnections of carbonyl containing molecules. There have been extensive reports of catalytic C(sp^2)–H carbonylation processes, with selective functionalisation typically occurring on the *ortho* positions of aromatic rings. However, reports of C(sp^3)–H carbonylation reactions are significantly less common and catalytic C(sp^3)–H carbonylation is still in its infancy. A number of issues specific to C–H carbonylation have been identified, perhaps the most important of which is carbon monoxide mediated palladium(II) catalyst reduction.[43,44,50,82,109] A number of strategies have been put forward to accelerate C–H activation event such that catalyst degradation by reduction is outcompeted.



Scheme 43: The widely accepted mechanistic blueprint for palladium-catalysed C–H carbonylation.

The majority of C–H carbonylation processes are proposed to occur *via* a common and widely accepted mechanistic blueprint, comprising of substrate binding, C–H activation to afford an organopalladium complex, 1,1-migratory insertion of carbon monoxide into the Pd–C bond and a final reductive elimination step (Scheme 43). However, this mechanistic blueprint imposes a crucial limitation to C–H carbonylation reactions; the desired C–H activation step can be in direct competition with deleterious β-hydride elimination of the bound substrate. While C–H activation can be faster than β-hydride elimination in some C(sp^2)–H carbonylations,[32,65] it can be a significant issue in other reactions.[33,82,120] In many cases, substrates for C–H carbonylation are often restricted to those that do not bear α-hydrogens to the directing group, such that β-hydride elimination cannot occur.

The impact of this crucial limitation of C–H carbonylation reactions can be illustrated by considering secondary aliphatic amines. To facilitate discussion, secondary aliphatic amines can be broadly divided into six structural sub-classes, with each sub-class differing by the degree of substitution on the carbons directly attached to the nitrogen atom (Figure 1).

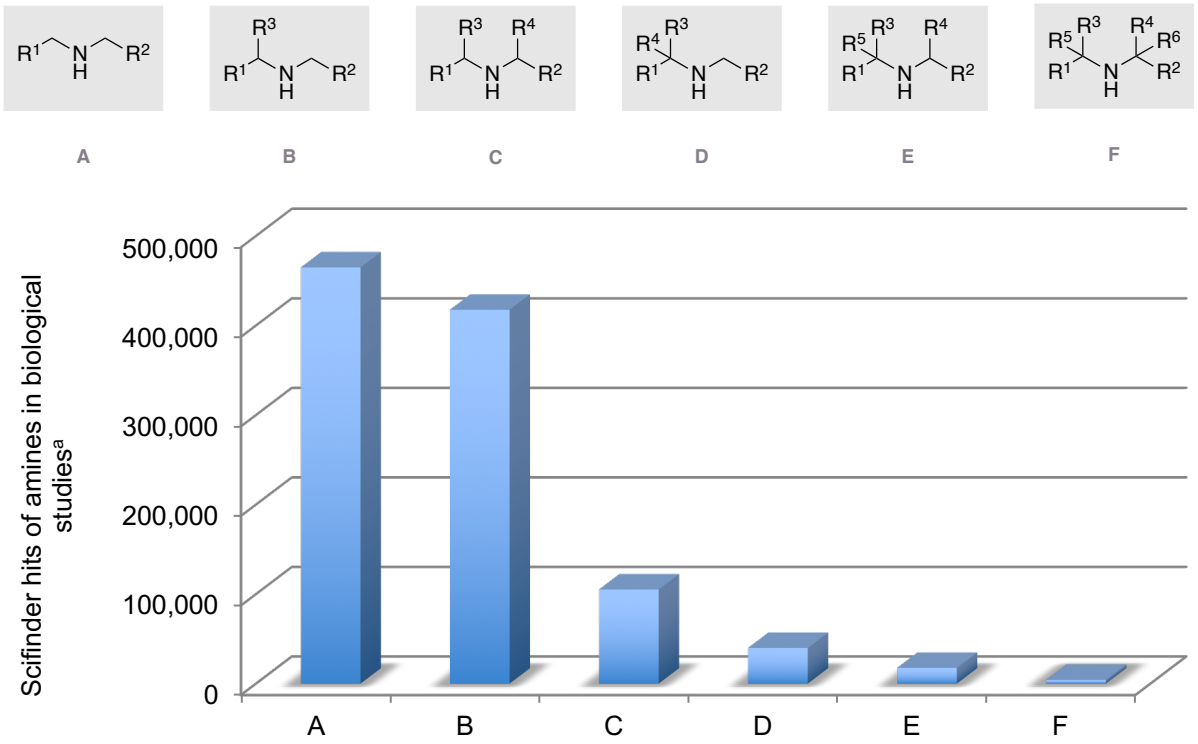
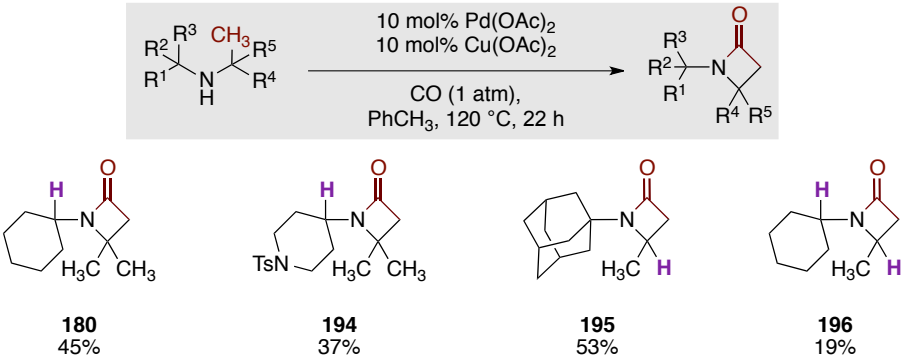


Figure 1: Structural sub-classes of secondary aliphatic amines and their prevalence in compounds with reported biological activity. [a)] Scifinder accessed 11/07/17

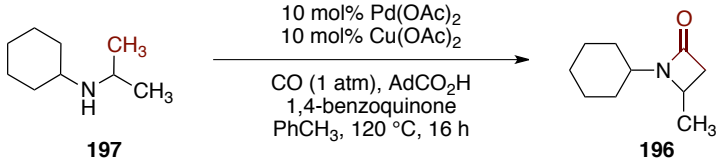
When the prevalence of each sub-class in biological studies is examined, it is evident that less-hindered secondary amines are most commonly investigated (Figure 1). Indeed, the 'Type F' amines that are amenable to existing C–H carbonylation methodology are virtually unexplored as pharmaceutical agents.[33] Before any reaction can find widespread application, it must tolerate substrates that are of interest to practitioners of synthetic and medicinal chemistry. To this end, preliminary work by the Gaunt group had established that a limited number of less substituted secondary aliphatic amines were amenable to palladium-catalysed C–H carbonylation, albeit in low yields (Scheme 44).[33]



Scheme 44: Selected examples of the C(sp^3)–H carbonylation of less subsituted secondary aliphatic amines.

Dr Darren Willcox subsequently built on these initial results and carried out an optimisation study on the C(sp^3)–H carbonylation of *N*-cyclohexylisopropylamine (Table 1); a summary of these experiments follows. The group's previous reaction could be reproduced to provide β-lactam **196** in 19% yield (Table 1, entry 1).[33] Performing the reaction under a balloon of carbon monoxide, rather than a 1:1 carbon monoxide/air mixture provided the β-lactam in identical yield (Table 1, entry 2). The addition of 50 mol% 1-adamantanecarboxylic acid, an additive reported to enhance C–H functionalisation reactions,[123–126] gave a modest increase in yield to 32% (Table 1, entry 3). A similar improvement was observed when the

initial reaction was conducted in the presence of 2.0 equivalents of 1,4-benzoquinone (Table 1, entry 4). Pleasingly, the combination of both additives gave a dramatic increase in yield, providing β-lactam **196** in 65% yield (Table 1, entry 5). Increasing the 1,4-benzoquinone loading further to 4.0 equivalents gave an additional improvement in yield to 81% (Table 1, entry 6).



197 **196**

entry	CO mix	$AdCO_2H$ /mol%	1,4-benzoquinone /equiv	yield of **196** /%[a]
1	CO/air (1:1)	0	0.0	19
2	CO	0	0.0	19
3	CO	50	0.0	32
4	CO	0	2.0	30
5	CO	50	2.0	65
6	CO	50	4.0	81

Table 1: Optimisation studies on the C(sp^3)–H carbonylation of *N*-cyclohexylisopropylamine **197** conducted by Dr Darren Willcox. [a)] Yield obtained by GC assay against a 1,1,2,2-tetrachloroethane internal standard.

With conditions allowing the efficient C(sp^3)–H carbonylation of this less hindered amine in hand, two questions were posed:

- Could this C(sp^3)–H carbonylation reaction be broadly applied to all sub-classes of secondary aliphatic amine?

- What is the mechanism of this C(sp^3)–H carbonylation reaction; is it distinct from existing processes?

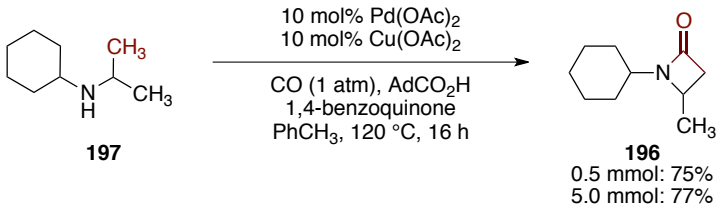
2. Results and Discussion

2.1 Establishing a robust C–H carbonylation protocol

From here on in, all described work is my own unless otherwise stated. Initial experiments sought to replicate the C–H carbonylation of *N*-cyclohexylisopropylamine under conditions developed by Dr Darren Willcox (Table 1). The reaction was found to be capricious, with large variation in yields observed (40-88%) across successive repeats. Before the substrate scope of the C–H carbonylation could be examined, a robust reaction protocol was required. Previous studies from within the Gaunt group had established that physical parameters, such as the stirring speed of the reaction mixture, could significantly affect the reproducibility of C–H carbonylation reactions.[33,127] Accordingly, the physical parameters of the C–H carbonylation reaction of *N*-cyclohexylisopropylamine were systematically studied (see experimental section 4.3 for more details). Important parameters for a 0.5 mmol scale reaction were found to be:

- Stirring rate (300 RPM)
- Stir bar size (1¼ inch egg shaped)
- Position in the oil bath (centred)
- Depth in oil bath (oil depth in bath set to 42 mm, reaction placed such that the oil and solvent level were equal)
- Reaction vessel (50 ml, B24 necked round bottomed flask fitted with B24 condenser)
- Purity of 1,4-benzoquinone (recrystallised from hexane, stored at room temperature)
- Purity of amine (purified by column chromatography and then purified by kugelrohr distillation)

As a result of these reliability studies, a robust reaction set up was identified on a 0.5 mmol scale that furnished β-lactam **196** in 81% NMR yield as determined by ^{1}H NMR assay against an internal standard of 1,1,2,2-tetrachloroethane, with a variation of ±1% across three successive repeats. Over the course of this optimisation process, repeated attempts to isolate β-lactam **196** resulted in significantly lower isolated yields than the corresponding assay yields. Ultimately, it was found that loading the reaction mixture directly onto silica gel allowed the isolation of β-lactam **196** by column chromatography in 75% yield (Scheme 45).



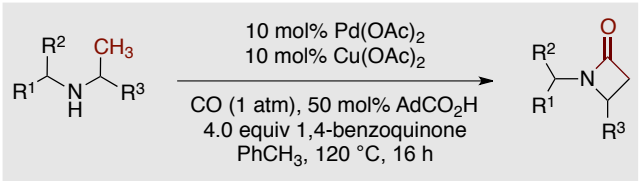
Scheme 45: C(sp^3)–H carbonylation of *N*-cyclohexylisopropylamine **197** on 0.5 mmol and 5.0 mmol scales

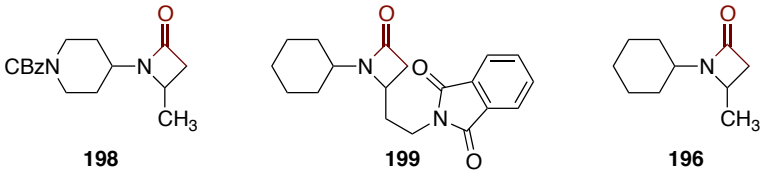
Whilst a 0.5 mmol scale C–H carbonylation reaction was sufficient for exploring the substrate scope, we were mindful that the low material throughput would limit this methodology's application to preparative synthesis. Accordingly, a reaction set up was established (500 ml B24 round bottomed flask fitted with B24 condenser, 2½ inch egg shaped stir bar, 225 RPM stir rate) that allowed the C–H carbonylation

reaction to be performed on a 5.0 mmol scale, producing β-lactam **196** in a comparable isolated yield of 77% (Scheme 45).

2.2 Further optimisation of the C-H carbonylation reaction

Having established a robust C–H carbonylation protocol, an initial substrate scope of the reaction was examined. The yields of β-lactams obtained under the optimised conditions were moderate (17 - 83%, mean 59%, see experimental section 4.4 for details), thus, further optimisation was required. The developed C–H carbonylation reaction procedure involved combining the reactants under an air atmosphere and then placing the reaction mixture under a balloon of carbon monoxide. The low solubility of carbon monoxide in organic solvents is well documented[45,46] and it was hypothesised that increasing the carbon monoxide content of the initial reaction atmosphere might have a beneficial effect. Accordingly, the C–H carbonylation reactions of three representative substrates was conducted under different initial atmospheres (Table 2).





198 **199** **196**

initial atmosphere	yield of **198** /%[a]	yield of **199** /%[a]	yield of **196** /%[a]
air	70	61	81
6.25% CO in air	77	69	79
pure CO	-	-	55

Table 2: The C–H carbonylation of three substrates set up under different initial atmospheres, before being placed under a balloon of carbon monoxide. [a)] Yields were obtained by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

Performing the C–H carbonylation under an initial atmosphere of 6.25% carbon monoxide in air gave a modest improvement in β-lactam yield for two substrates (**198** and **199**, Table 2), with a negligible effect on the third (**196**). Conducting the C–H carbonylation under an initial atmosphere of pure carbon monoxide had a deleterious effect on the reaction (**196**), presumably as air is required for the oxidation of the spent copper acetate co-catalyst.[128] As mixtures of carbon monoxide and air at intermediate concentrations between 6.25% and 100% are not commercially available, further optimisation of the reaction's initial atmosphere was not possible. Thus, from this point forward, C–H carbonylations were backfilled with 6.25% carbon monoxide in air (× 3) and then placed under a balloon of carbon monoxide that was filled to a volume of approximately 500 ml.

A timecourse study of the C–H carbonylation of *N*-cyclohexylisopropylamine **197** demonstrated that this reaction ceased to produce product after 6 hours (Figure 2). However, the other two substrates (**198** and **199**, Table 2) examined in this study were found to require reaction times between 16 h and 24 h to achieve full conversion.

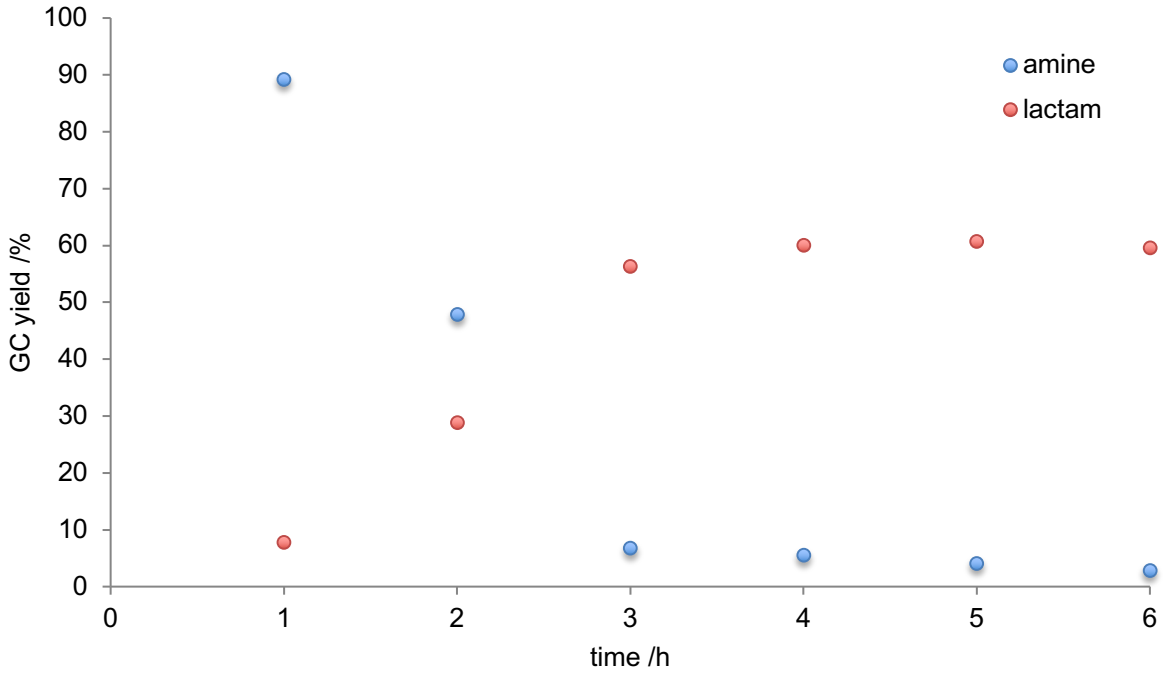
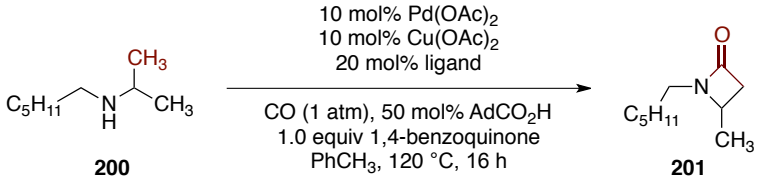


Figure 2: A graph to show the reaction profile for the C–H carbonylation of *N*-cyclohexylisopropylamine **197**. Yields were determined by GC assay against an internal dodecane internal standard.

In a parallel optimisation study of the C–H carbonylation of *N*-isopropylhexylamine **200**, Dr Darren Willcox had conducted an extensive ligand screen and found that the addition of 20 mol% of Li-quinoline provided improved yields of β-lactam **201** (Table 3).[129]

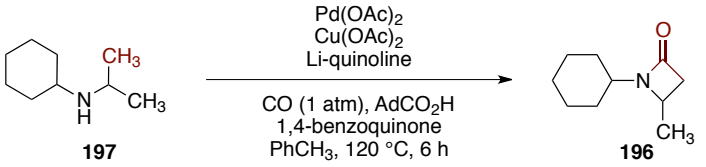


ligand	yield of **201** /%[a]
none	17
xantphos	20
norbornene	21
pyridine	26
2,6-lutidine	16
4-methoxypyridine	9
acridine	24
Li-quinoline	33

Table 3: The effect of ligands on the C–H carbonylation of *N*-isopropylhexylamine conducted by Dr Darren Willcox. [a)] Yields determined by GC against a 1,1,2,2-tetrachloroethane internal standard.

Encouraged by these results, the effect of Li-quinoline on the C–H carbonylation of *N*-cyclohexylisopropylamine **197** was investigated (Table 4). The addition of 10 mol% Li-quinoline to the standard reaction conditions resulted in an increase in β-lactam **196** yield (Table 4 entries 1 & 2). In the presence of ligand, the loading of 1,4-benzoquinone could be decreased from 4.0 equivalents to just 1.0 equivalent, without a dramatic impact on reaction performance (Table 4, entry 3). The loadings of palladium acetate, copper acetate and 1-adamantanecarboxylic acid could be halved to provide the β-lactam in a comparable yield (Table 4, entry 4); reducing the loading of copper acetate was found to be detrimental to the reaction (Table 4, entry 5). Attempts to further decrease the loading of 1-

adamantanecarboxylic acid were also found to be detrimental to the reaction (Table 4, entries 6 to 9). The optimal reaction conditions were thus established as requiring a 0.1M toluene (with respect to amine) solution of 5 mol% palladium acetate, 10 mol% copper acetate, 5 mol% Li-quinoline, 1.0 equivalent of 1,4-benzoquinone and 25 mol% 1-adamantanecarboxylic acid to be backfilled with 6.25% carbon monoxide in air, before being placed under a balloon of carbon monoxide and stirring for 6 h at 120 °C (Table 4, entry 4). Under these optimal conditions, β-lactam **196** could be isolated in 82% yield.



entry	$Pd(OAc)_2$ /mol%	$Cu(OAc)_2$ /mol%	Li-quinoline /mol%	$AdCO_2H$ /mol%	1,4-benzoquinone /equiv	yield of **196** /%[a]
1	10	10	0	50	4.0	81
2	10	10	10	50	4.0	89
3	10	10	10	50	1.0	83
4	5	10	5	25	1.0	82
5	5	5	5	25	1.0	58
6	5	10	5	5	1.0	47
7	5	10	5	10	1.0	75
8	5	10	5	15	1.0	72
9	5	10	5	20	1.0	69

Table 4: Further optimisation of the C–H carbonylation of *N*-cyclohexylisopropylamine **197** by the addition of Li-quinoline. [a)] Yields determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

2.3 Establishing the scope and limitations of the C-H carbonylation

To facilitate discussion of substrates within the project, secondary aliphatic amines were divided into five structural sub-classes (Figure 3), with each sub-class differing by the degree of substitution on the carbons directly attached to the nitrogen atom.

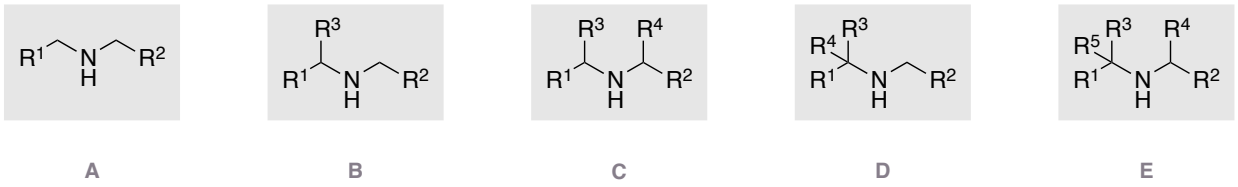


Figure 3: Structural sub-classes of secondary aliphatic amines.

A range of 'Class C' amines could be readily prepared by standard methods in 1 – 3 steps from commercially available materials. The optimised conditions developed during these studies were applied to the C–H carbonylation of a diverse array of 'Class C' secondary aliphatic amines (Scheme 46). *N*-cyclopentyl (**203**), *N*-cyclohexyl (**196**) and *N*-cycloheptyl (**202**) alicycles were tolerated in the C–H carbonylation, with *N*-cyclohexyl substituent providing the best results. Diisopropylamine, a bulk industrial chemical,[130] was found to undergo smooth C–H carbonylation to afford β-lactam **204** in 61% yield. In the case of *N*-(*sec*-butyl)cyclohexylamine, exclusive β-C–H carbonylation of the methyl substituent was observed providing β-lactam **205**; competitive γ-C–H carbonylation of the ethyl substituent was not observed.

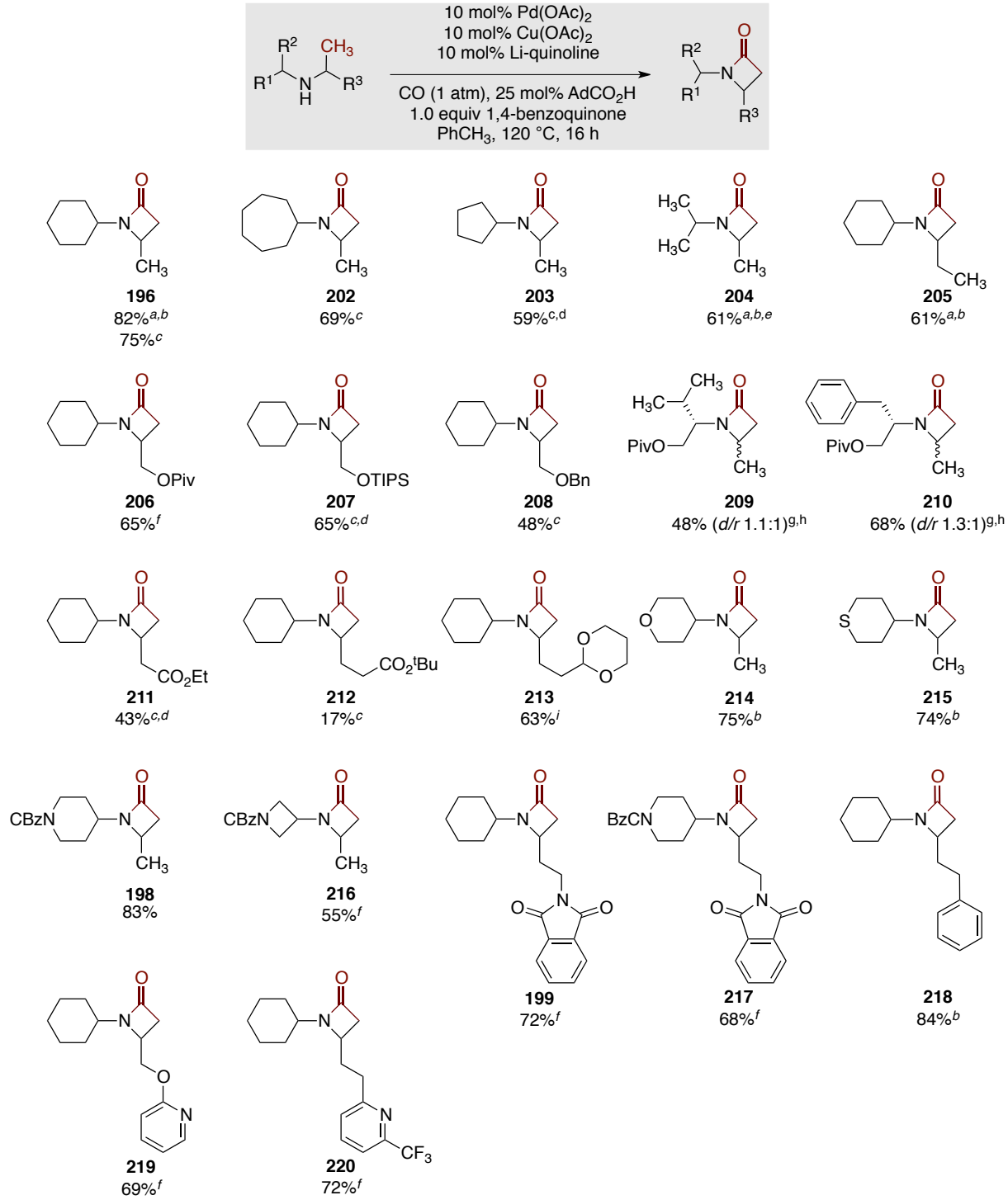
The tolerance of functional groups containing heteroatoms was next investigated. 1,2-Amino alcohols are versatile synthetic intermediates,[131] are widely found in natural products[131] and are an important class of ligands in transition metal catalysis.[132] We were, therefore, pleased to observe that *O*-pivaloyl (**206**), *O*-triisopropylsilyl (**207**) and *O*-benzyl (**208**) protected 1,2-amino alcohol-derived substrates worked well in the C–H carbonylation. However, other hydroxyl-protecting groups including *O*-methoxymethyl, *O*-methyl and *O*-*tert*-butyldimethylsilyl were not tolerated and returned starting material. The C–H carbonylation was applied to *O*-protected *N*-isopropyl derivatives of 1,2-amino alcohols derived from natural amino acids (e.g. **209** and **210**) and β-lactam products were obtained in 48 – 93% yield, but only modest levels of diastereoselectivity were observed. Unfortunately, extensive screening of ligands, carboxylic acid additives and substrates did not allow an increase in diastereoselectivity to be observed (see experimental section 4.8 for more details). Secondary amines derived from β- and γ-amino acid esters were also competent substrates for the carbonylation reaction, although gave poor to moderate yields of the corresponding β-lactams (**211** and **212**). It was found that a substrate containing a acetal protected aldehyde was tolerated in the C–H carbonylation reaction (**213)**, with the best yields being obtained in the presence of Li_2CO_3. It is assumed that Li_2CO_3 buffers the reaction and prevents hydrolysis of the acid sensitive acetal group.[133]

Saturated heterocycles are increasingly popular motifs in pharmaceutical chemistry due to their attractive physical properties.[134] Pleasingly, secondary amine substrates containing saturated heterocycles were amenable to C–H carbonylation reaction and afforded the corresponding β-lactams in good yields (**214**, **215** and **198**). Even a substrate containing a tetrahydrothiopyran ring worked well in the C–H carbonylation reaction. This result is striking as thioethers are commonly found to poison palladium(II) catalysts and inhibit catalytic activity.[135] Moreover, thioethers are readily oxidised to sulfoxides and sulfones,[136] however, this was not observed to be an issue in the C–H carbonylation reaction; side products derived from thioether oxidation could not be detected.

A substrate containing a CBz protected azetidine underwent C–H carbonylation to provide β-lactam **216**, which contains two strained nitrogen heterocycles. Both azetidines and β-lactams are considered to be important motifs in the preparation of biologically active molecules.[137–140] A substrate containing a primary amine, protected as a phthalimide, was also tolerated in the C–H carbonylation reaction to give β-lactam **199** in good yield. Aliphatic amines are common in pharmaceutical agents and we were therefore keen to exemplify the C–H carbonylation on a substrate containing multiple amine motifs.[119] Accordingly, a substrate containing two differentially protected amines, a CBz protected piperidine and a primary amine protected as a phthalimide, was subjected to the carbonylation reaction, providing β-lactam **217** in 68% yield.

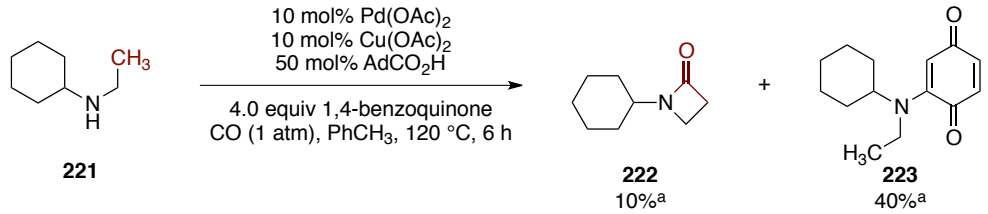
Fujiwara had previously reported the undirected C(sp^2)–H carbonylation of arenes.[50] It was therefore a concern that, under our conditions, amine substrates containing aryl rings would succumb to competitive C–H carbonylation of the arene. However, an amine substrate with a pendent aryl ring was found to undergo exclusive β-C(sp^3)–H carbonylation at the methyl group to provide β-lactam **218** in excellent yield; competitive ε-C(sp^2)–H carbonylation of the aryl ring was not observed. Heteroaromatics, such as pyridines, have been demonstrated to act as competent directing groups for palladium-catalysed C–H

carbonylation reactions.[92,94,95,96] We were, therefore, delighted to observe that pyridine-containing substrates were well tolerated in the C–H carbonylation reaction (**219** and **220**), without products derived from the pyridine-directed reaction being observed.



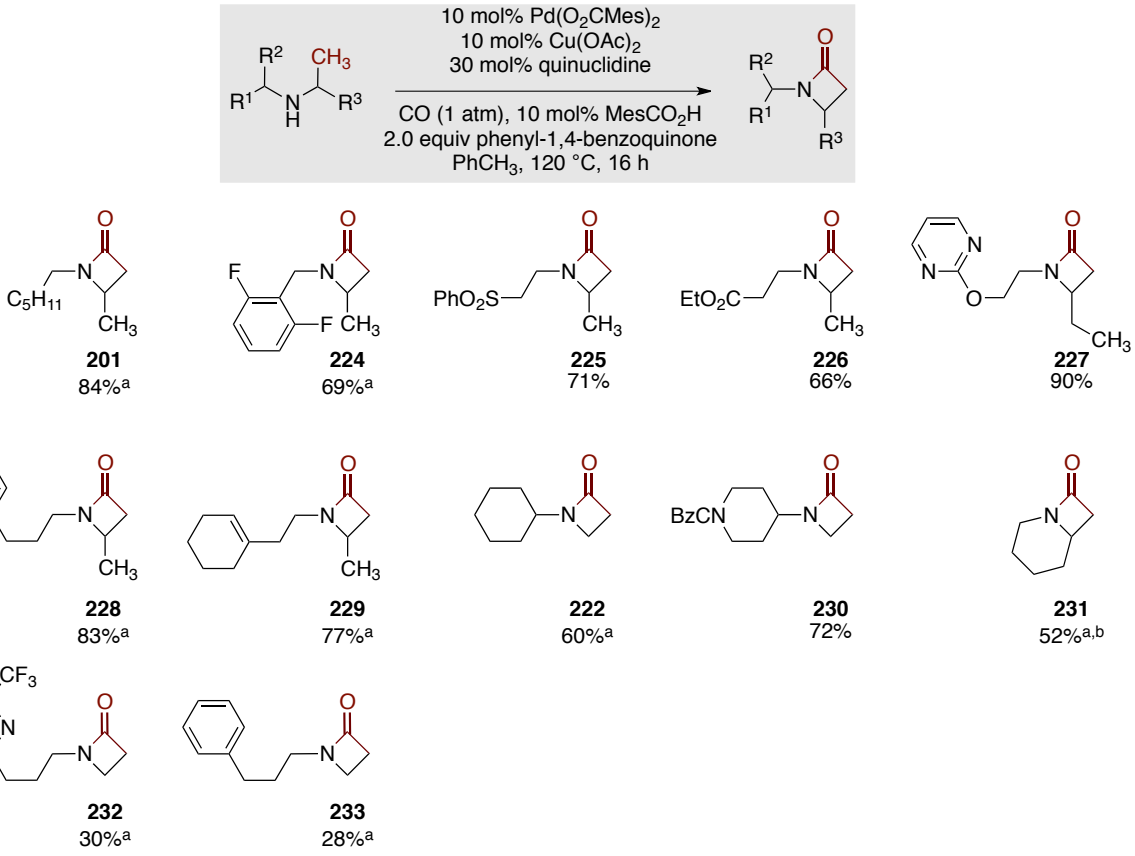
Scheme 46: The scope of the C–H carbonylation of 'Class C' secondary aliphatic amines. Reactions performed under standard conditions unless otherwise specified: [a] 5 mol% $Pd(OAc)_2$, 5 mol% Li-quinoline; [b] 6 h; [c] 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, 50 mol% $AdCO_2H$, 4.0 equiv 1,4-benzoquinone; [d] performed by Dr Darren Willcox; [e] 100 °C; [f] 2.0 equiv 1,4-benzoquinone; [g] Li-quinoline was replaced with pyridine; [h] ^1H NMR yield against 1,1,2,2-tetrachloroethane internal standard; [i] 2.0 equiv Li_2CO_3 was added.

When *N*-ethylcyclohexylamine **221**, a less hindered, 'Class B' amine, was subjected to these reaction conditions, β-lactam **222** was observed in 10% yield by ^{1}H NMR assay, with concomitant formation of side product **223** in 40% yield (Scheme 47). The oxidative amidation of 1,4-benzoquinone with secondary aliphatic amines is known, [141,142] and it is believed that this pathway is responsible for the formation of side product **223**.



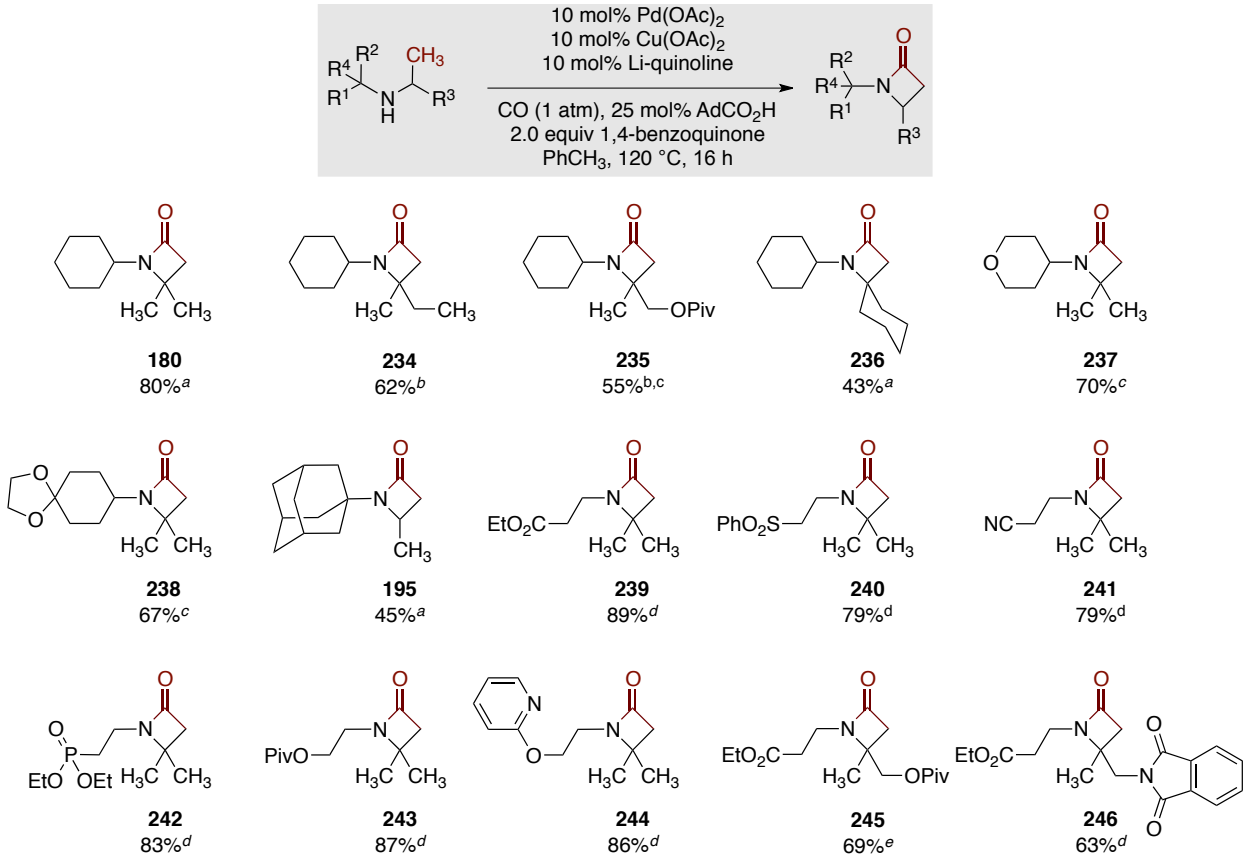
Scheme 47: Initial C–H carbonylation of *N*-ethylcyclohexylamine **221**. [a)] Yields determined by 1H NMR assay against a 1,1,2,2-tetrachloroethane internal standard.

After an extensive optimisation procedure, Dr Darren Willcox discovered that this side reaction could be suppressed by employing phenyl-1,4-benzoquinone in the C–H carbonylation instead of 1,4-benzoquinone. It was also found that the addition of 2-mesitylenecarboxylic acid and a quinuclidine ligand were important for high yields of β-lactam. After establishing these conditions, Dr Darren Willcox went on to explore the scope of the C–H carbonylation of 'Class A' and 'Class B' aliphatic amines (Scheme 48). In addition to the functional group tolerance demonstrated within the C–H carbonylation of 'Class C amines', it was also found that sulfone (**225**), pyrimidine (**227**) and alkene (**229**) substituents were also accepted. Furthermore, it was demonstrated that a cyclic amine could direct C–H carbonylation to afford a 4,6-fused bicyclic β-lactam **231**.



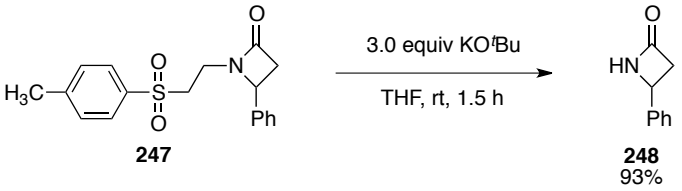
Scheme 48: The scope of the C–H carbonylation of 'Class A' and 'Class B' amines performed by Dr Darren Willcox. Reactions performed under standard conditions unless otherwise specified: [a)] 3 h; [b)] 0.3 mmol scale.

Kirsten Hogg and Dr Jonas Calleja demonstrated that the above reaction conditions, with either Li-quinoline or quinuclidine additives, could be applied to the C–H carbonylation of more hindered 'Class D' and 'Class E' secondary aliphatic amines (Scheme 49). It was found that a number of 'Class E' substrates benefitted from the addition of 3.0 equivalents of silver pivalate, which presumably facilitates the oxidation of palladium(0) in order to regenerate the palladium(II) catalyst. In addition to the functional group tolerance established in previous substrate classes, nitrile (**241**) and phosphonate (**242**) substituents were also accepted on the amine substrates. Spirocycles are interesting three-dimensional structures that have attracted considerable interest from the pharmaceutical industry.[143] Pleasingly, a spirocyclic β-lactam (**236**) could be accessed by palladium-catalysed C–H carbonylation, albeit in moderate yield.



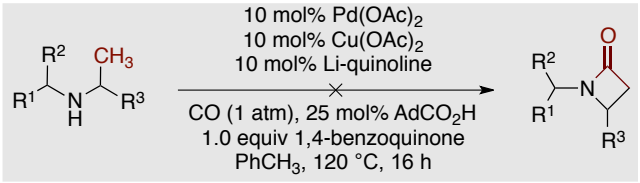
Scheme 49: The scope of the C–H carbonylation of 'Class D' and 'Class E' secondary aliphatic amines performed by Kirsten Hogg and Dr Jonas Calleja respectively. Reactions performed under standard conditions unless otherwise specified: [a] 5 mol% $Pd(OAc)_2$, 5 mol% Li-quinoline, 1.0 equiv 1,4-benzoquinone, [b] 3.0 equiv AgOPiv was added; [c] 0.2 mmol scale; [d] 10 mol% $Pd(O_2CMes)_2$, 10 mol% $Cu(OAc)_2$, 30 mol% quinuclidine, 10 mol% $MesCO_2H$, 2.0 equiv phenyl-1,4-benzoquinone; [e] 1,4-benzoquinone was replaced with phenyl-1,4-benzoquinone

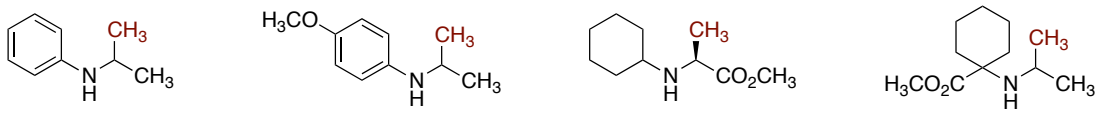
Furthermore, it has been shown by Weinreb that *N*-tosylethyl substituents can be cleaved from β-lactams to provide the free NH-β-lactams (Scheme 50).[144] One would, therefore, expect that β-lactam **240** (Scheme 49) could undergo a retro-Michael reaction under basic conditions to furnish the NH-β-lactam and phenylvinylsulfone. This sulfone substituent could thus be used as a protecting group for primary amines in the C–H carbonylation reaction.

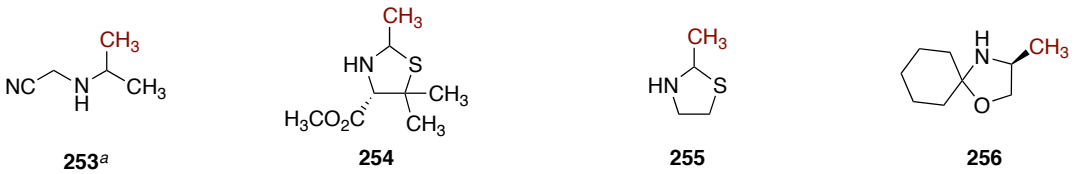


Scheme 50: Cleavage of Weinreb's *N*-tosylethyl protecting group for β-lactams

The C–H carbonylation was found to be remarkably tolerant of many different functional groups, however, the reaction was not without its limitations (Scheme 51). *N*-Isopropylanilines were unsuccessful in the C–H carbonylation and returned starting material (**249** and **250**). α-Amino esters were not tolerated and starting material was unreacted, regardless of whether the targeted methyl group was proximal (**251**) or distal (**252**) to the carbonyl group. This suggests that the intolerance of these substrates is not an effect of C–H bond acidity. It was disappointing that these substrates were not tolerated as the α-amino acid motif is an essential part of the pharmacophore of β-lactam antibiotics and is involved in D-alanyl-D-alanine carboxypeptidase binding.[145] The C–H carbonylation of **254** would be important, as it would provide rapid access to penicillin scaffolds.[146] However, when the carbonylation of **254** was attempted under conditions established in this study, the reaction returned only starting material. Thiazolidine **255** and oxazolidine **256** were consumed under the C–H carbonylation reaction conditions, but did not afford detectable products, suggesting decomposition.

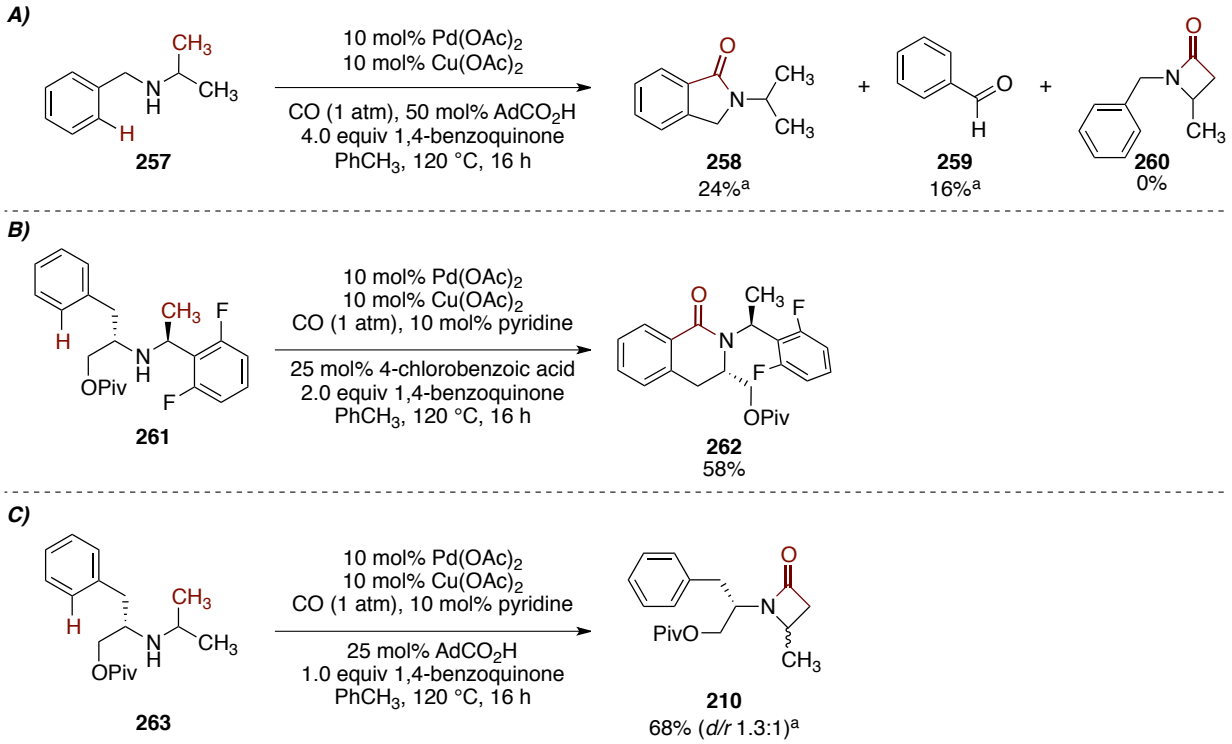






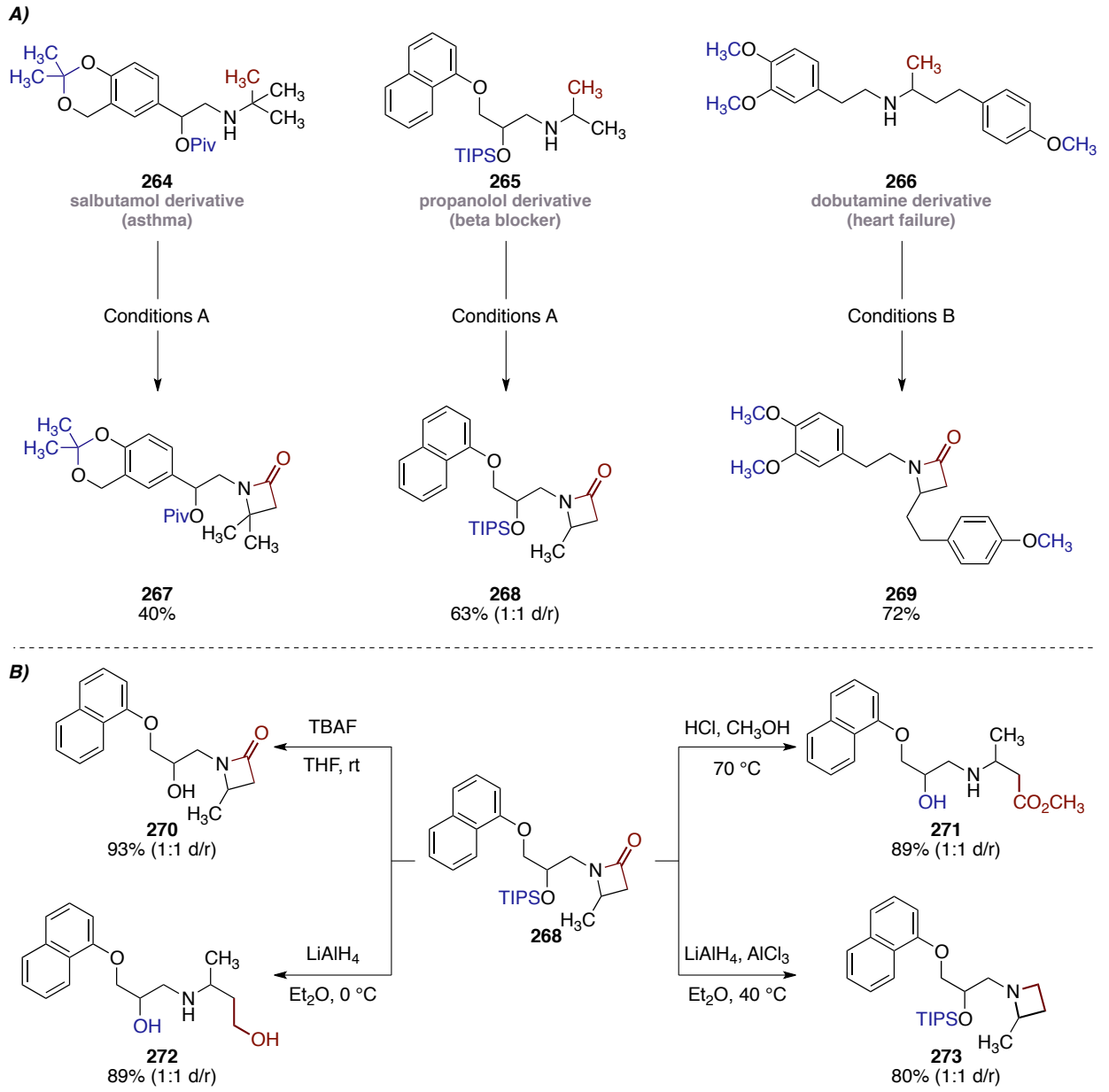
Scheme 51: A selection of aliphatic amines that were not tolerated in the C–H carbonylation reaction. [a] Reaction performed by Dr Darren Willcox

Competitive C(sp^2)–H carbonylation was observed in substrates that contained an aryl ring proximal to the nitrogen, such that amine directed C(sp^2)–H activation could result in a five-membered palladacycle (Scheme 52).[32,63] For example, benzylamine **257** afforded the corresponding benzolactam in 24% yield without observation of the β-lactam (Scheme 52, A). Similarly, the carbonylation of phenethylamine **261** was hampered by C(sp^2)–H carbonylation and afforded benzolactam product in 58% yield, presumably *via* a six-membered palladacycle (Scheme 52, B). However, in a related example, the carbonylation of phenethylamine **263** was observed to provide access to β-lactam, without the products from C(sp^2)–H carbonylation being observed (Scheme 52, C). This demonstrates that C(sp^2)–H carbonylation *via* a six-membered palladacycle can be outcompeted by C(sp^3)–H carbonylation in some cases.



Scheme 52: The C–H carbonylation of benzylamine and phenethylamine substrates. **A)** C(sp^2)–H carbonylation of a secondary benzylamine; **B)** C(sp^2)–H carbonylation of a phenethylamine substrate; **C)** C(sp^3)–H carbonylation of phenethylamine substrate, in which products from C(sp^2)–H carbonylation were not observed. [a)] Yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

Reactions that work on complex molecules can enable the late diversification of lead compounds and thus have the potential to accelerate the lead-optimisation phase of drug discovery.[147] The remarkable functional group tolerance of the C–H carbonylation reaction described in this work, coupled with the abundance of secondary aliphatic amines in medicinal compounds,[119] suggested that this C–H carbonylation methodology could be broadly applied to biologically active amines as a late-stage diversification tactic. Accordingly, Dr Jonas Calleja and Dr Darren Willcox subjected a selection of pharmaceutical derivatives to the C–H carbonylation reaction (Scheme 53, A). The synthetic utility of the β-lactam products was then demonstrated and downstream chemistry of the β-lactam motif provided access to β-amino alcohol (**272**), azetidine (**273**) and ester (**271**) functionality (Scheme 53, B). Furthermore, it was demonstrated that TIPS alcohol protecting group employed in this salbutamol derivative could be cleaved to provide access to the unprotected β-lactam (**270**).



Scheme 53: Application of the C–H carbonylation reaction as a late-stage diversification strategy. **A)** The C–H carbonylation of pharmaceutical derivatives; Conditions A = 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, 10 mol% Li-quinoline, 25 mol% $AdCO_2H$, 2.0 equiv 1,4-benzoquinone; Conditions B = 10 mol% $Pd(O_2CMes)_2$, 10 mol% $Cu(OAc)_2$, 30 mol% quinuclidine, 10 mol% $MesCO_2H$, 2.0 equiv phenyl-1,4-benzoquinone. **B)** Derivatisations of the β-lactam framework; TBAF, tetrabutylammonium fluoride; TIPS, triisopropylsilyl; d/r, diastereomeric ratio.

In summary, it was found that the developed C–H carbonylation reaction could be broadly applied to a diverse range of secondary aliphatic amines. The reaction was remarkably tolerant of functional groups and even accepted functionalities that typically cause issues in palladium-catalysed C–H activation reactions such as heteroaromatics (**219**, **220, 227**) and thioethers (**215**). A key improvement on previously established methodology was that amines that can undergo β-hydride elimination were amenable to the reaction.[33,120] Secondary aliphatic amines across a broad range of structural sub classes underwent C(sp^3)–H carbonylation, ranging from 'Type E' amines bearing one α-hydrogen to nitrogen to 'Type A' amines bearing four α-hydrogens to nitrogen. Finally, the C–H carbonylation reaction was applied as a late-stage diversification reaction of biologically relevant amines and the versatility of the β-lactam products allowed access to a number of analogues. My contributions to this synthetic work include

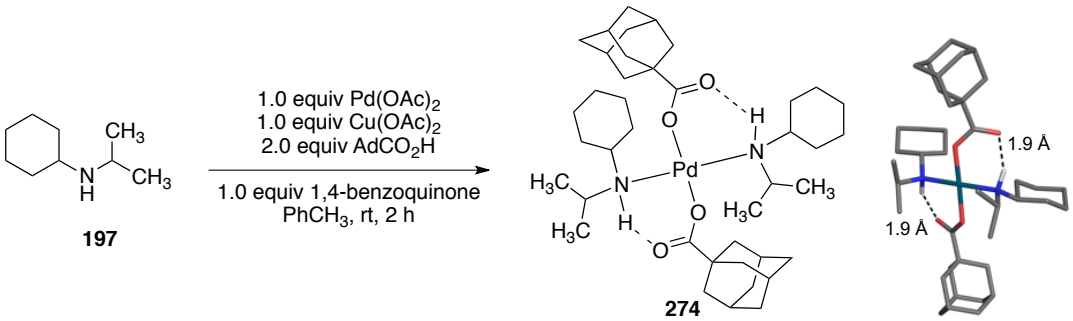
establishing a robust reaction protocol, some further optimisation of the reaction and exploring the scope and limitations of the C–H carbonylation of 'Class C' amines.

2.4 Elucidating the mechanism of the C–H carbonylation reaction

2.4.1 Assessing the feasibility of a four-membered palladacycle

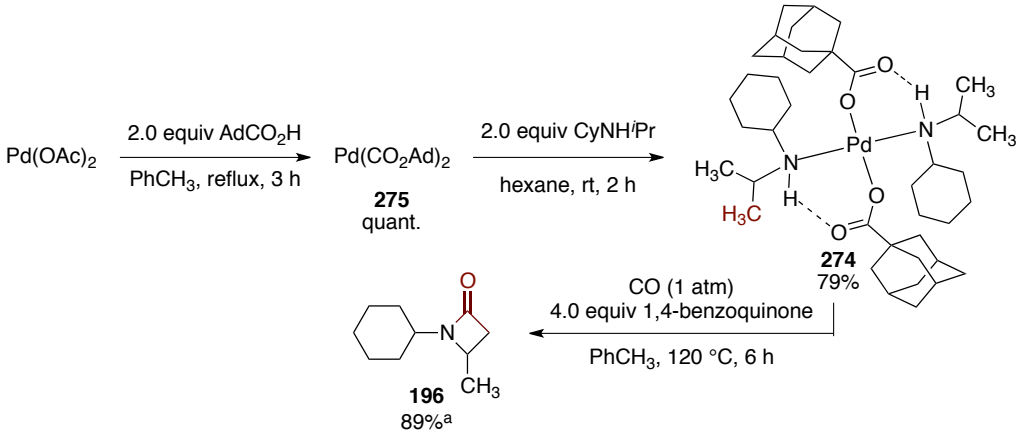
Having demonstrated the broad synthetic utility of the C(sp^3)–H carbonylation of secondary aliphatic amines, we wished to understand the reaction's mechanism. We were particularly keen to establish how the C(sp^3)–H carbonylation reaction had seemingly outcompeted β-hydride elimination, which had been observed to be a significant issue in previous methodology.[33,82,120]

In the hope of identifying the initial intermediate formed within the reaction, the components of the C–H carbonylation reaction, with the exception of carbon monoxide, were combined in toluene and stirred at room temperature for two hours. The reaction mixture was filtered through Celite™ and concentrated to provide a crude mixture, which was dissolved in CH_2Cl_2 and allowed to slowly evaporate with the hope of obtaining crystals suitable for x-ray crystallography. An x-ray crystal structure of bisamine palladium di-1-adamantoate **274** was obtained, in which there were hydrogen-bonding interactions between the amine and carboxylate ligands (Scheme 54).[148]



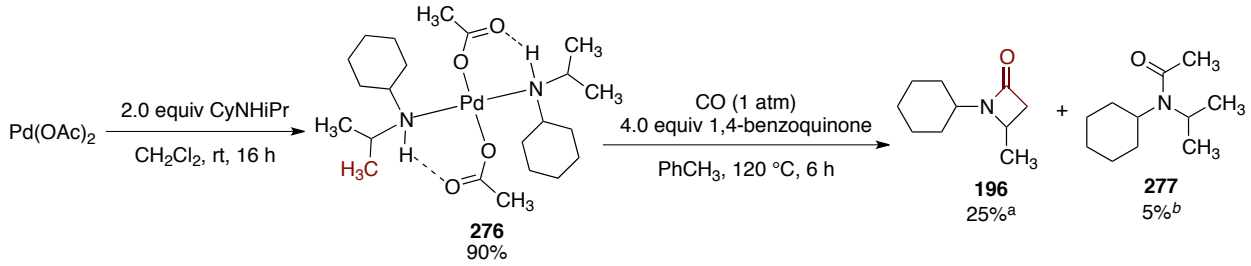
Scheme 54: A crystal structure of bisamine palladium di-1-adamantoate **274** obtained from a crude reaction mixture.

A scalable synthesis of bisamine palladium di-1-adamantoate **274** was developed and the complex was then subjected to C–H carbonylation conditions, resulting in the formation of β-lactam **196** in 89% yield with respect to palladium (Scheme 55). This demonstrates that bisamine complex **274** may be an intermediate in the C–H carbonylation reaction.



Scheme 55: A scalable synthesis of bisamine palladium di-1-adamantoate **274** and its subsequent C–H carbonylation. [a)] Yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

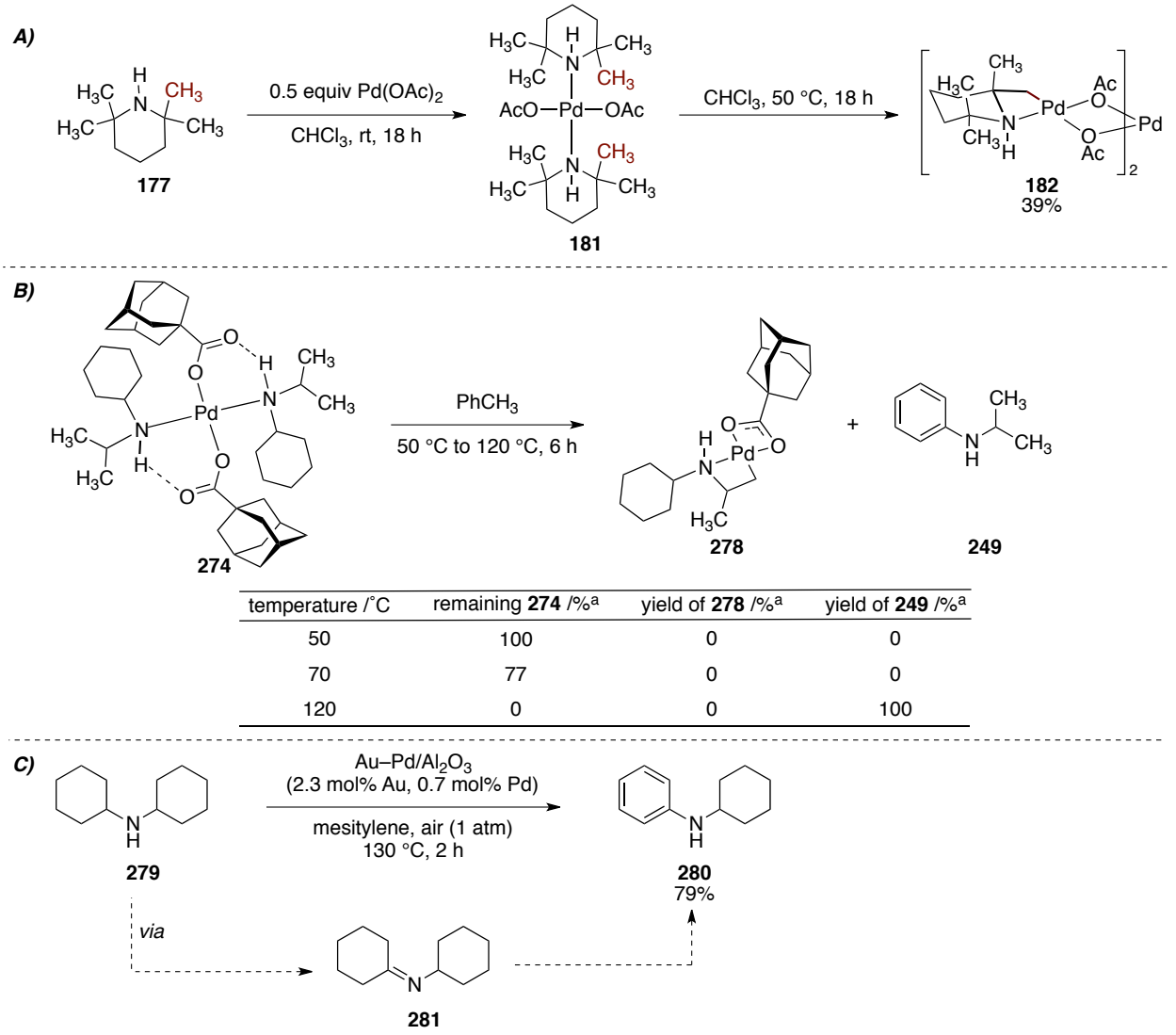
For comparison, the corresponding bisamine palladium diacetate complex **276** was synthesised from palladium acetate and amine **197**, and subjected to C–H carbonylation conditions (Scheme 56). In this case, β-lactam **196** was obtained in only 25% yield with respect to palladium and an acetamide byproduct **279** was also observed in 5% yield. Unfortunately, it was not possible to account for the remainder of the mass balance.



Scheme 56: The synthesis and C–H carbonylation of bisamine **276**. [a)] Yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard; [b)] Yield determined by GC against a dodecane internal standard.

These stoichiometric experiments demonstrate that a 1-adamantoate ligand is important in securing the effective C–H carbonylation of amine **197**, which has hydrogens on the α position to the amino group. In the catalytic C–H carbonylation, it is likely that 1-adamantanecarboxylic acid generates palladium di-1-adamantoate *in situ*. Furthermore, amide byproducts were not observed in the C–H carbonylation of bisamine palladium di-1-adamantoate **274**, suggesting that the 1-adamantoate ligand shuts down the side reaction responsible for amide formation.

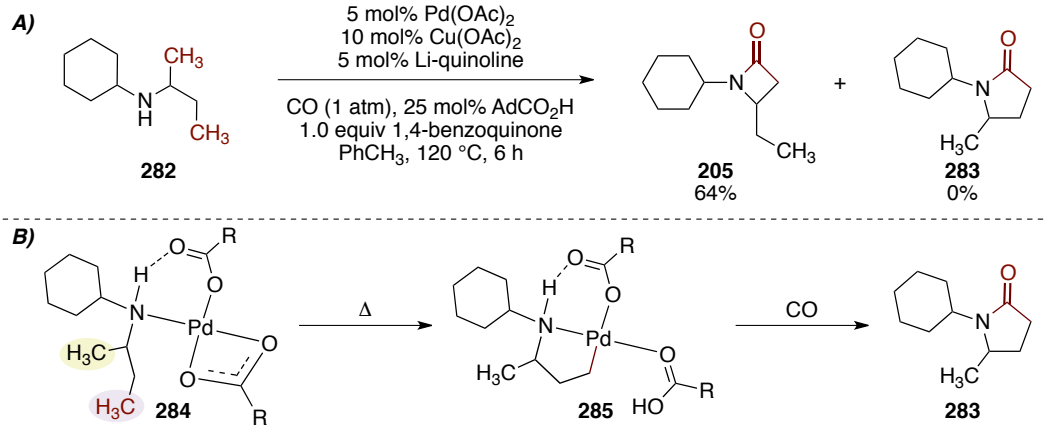
Previously within our group, a bisamine complex **181** had been demonstrated to form four-membered palladacycle **182** when heated at 50 °C (Scheme 57, A).[33] In order to examine the feasibility of a four-membered palladacycle intermediate in the C–H carbonylation reaction of Class C amines, bisamine palladium complex **274** was stirred at various temperatures in toluene (Scheme 57, B). The formation of a four-membered palladacycle was not observed in reactions at any of the examined temperatures. At 50 and 70 °C, the bisamine complex was observed to be unchanged. At 120 °C, degradation of the bisamine complex was observed, resulting in the quantitative formation of both aniline **249** and the *N*-cyclohexylisopropylamine 1-adamantanecarboxylic acid salt. It can be hypothesised that heating the bisamine complex **274** at this temperature results in amine ligand dissociation to form the corresponding monoamine complex, which subsequently undergoes β-hydride elimination to afford an imine. This imine is then presumably oxidatively aromatised to afford aniline **249**. Indeed, the palladium-mediated oxidative aromatisation of cyclohexylamines to afford anilines has been reported by Mizuno (Scheme 57, C).[149]



temperature /°C	remaining **274** /%[a]	yield of **278** /%[a]	yield of **249** /%[a]
50	100	0	0
70	77	0	0
120	0	0	100

Scheme 57: Cyclopalladation studies of bisamine palladium complexes. **A)** Gaunt's four-membered cyclopalladation of bisamine **181**; **B)** Unsuccessful attempts to form a four-membered palladacycle from bisamine **274**. [a)] Yields determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard; **C)** Mizuno's oxidative aromatisation of cyclohexylamines.

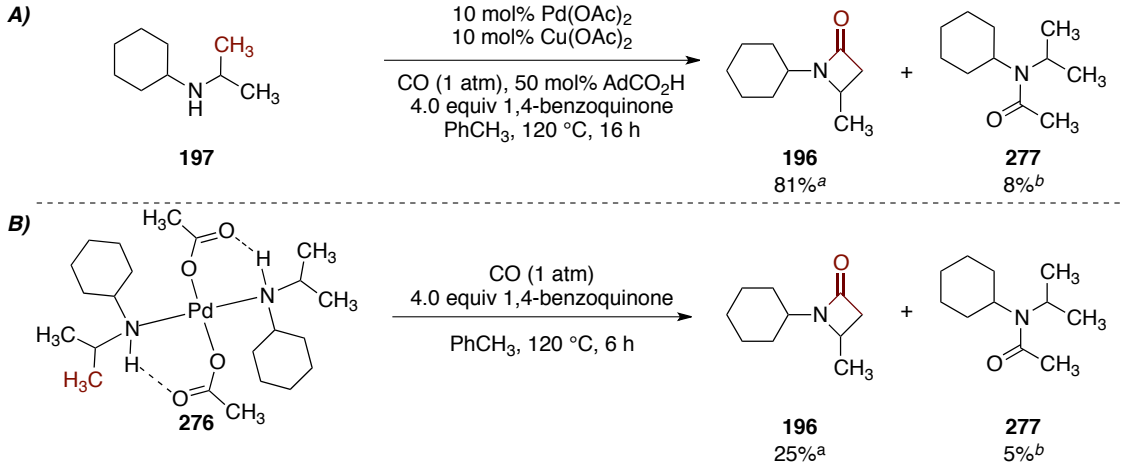
The inability to observe the formation of a four-membered palladacycle suggested that the pathway to the β-lactam products might not proceed *via* a traditional C–H carbonylation mechanism. In addition to these stoichiometric experiments, the catalytic C–H carbonylation of amine **282** (Scheme 58, A) cast further doubt on the intermediacy of a four-membered palladacycle. Amine **282** could undergo classical cyclopalladation on either the β-C–H bond of the methyl substituent (leading to a four-membered palladacycle) or the terminal γ-C–H bond in the ethyl substituent (resulting in a five-membered palladacycle). As cyclopalladation to form five-membered palladacycles is usually kinetically favoured over other ring sizes,[26,27] one would expect activation of the ethyl substituent to result, leading to γ-lactam **283** (Scheme 58, B). However, the C–H carbonylation of amine **282** was found to exclusively provide β-lactam **205** (Scheme 58, A), which is inconsistent with a traditional C–H carbonylation mechanism. With a traditional C–H carbonylation mechanism seeming improbable, we considered alternative mechanistic pathways by which C–H carbonylation could operate.



Scheme 58: The C–H carbonylation of amine **282**. **A)** Selective catalytic reaction to form β-lactam; **B)** Expected reaction pathway according to a traditional C–H carbonylation mechanism leading to γ-lactam.

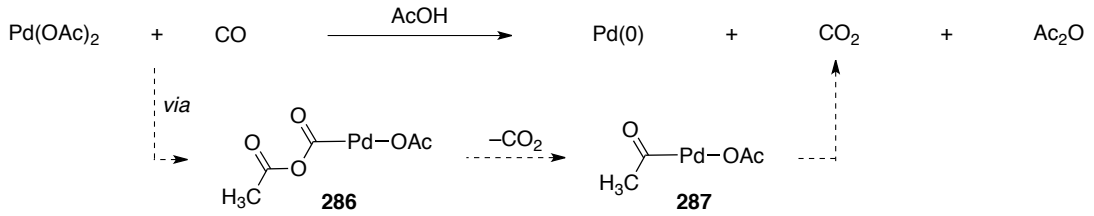
2.4.2 Understanding the formation of acetamide side products

In both catalytic (Scheme 59, A) and stoichiometric (Scheme 59, B) C–H carbonylation reactions, an acetamide side product (**277**) had been identified. Indeed, small quantities of *N*-acetylated side products were routinely observed by gas chromatography during the scope and limitation studies. This is perhaps unsurprising; both Grannel[66] and Zhu[75] have observed *N*-acetylated side products in the C–H carbonylation reactions of amines and anilines respectively.



Scheme 59: The formation of an acetamide byproduct in: **A)** the catalytic C–H carbonylation of **197**; **B)** the stoichiometric C–H carbonylation of bisamine **276**. [a)] Yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard; [b)] Yield determined by GC against a dodecane internal standard.

Moiseev had previously reported the reaction of palladium acetate and carbon monoxide to afford palladium(0), carbon dioxide and acetic anhydride (Scheme 60).[44] This process could be operative in our catalytic C–H carbonylation reaction of aliphatic amines and the generated acetic anhydride could react with amines to provide the *N*-acetylated side products. After detailed kinetic studies in an acetic acid solvent,[150] Moiseev tentatively proposed that the decomposition of palladium acetate involved carbon monoxide insertion into a Pd–OAc bond to furnish a palladium anhydride intermediate (**286**, Scheme 60). This palladium anhydride intermediate was proposed to rapidly extrude carbon dioxide to afford an acyl palladium intermediate (**287**), which after C–O reductive elimination gives acetic anhydride.

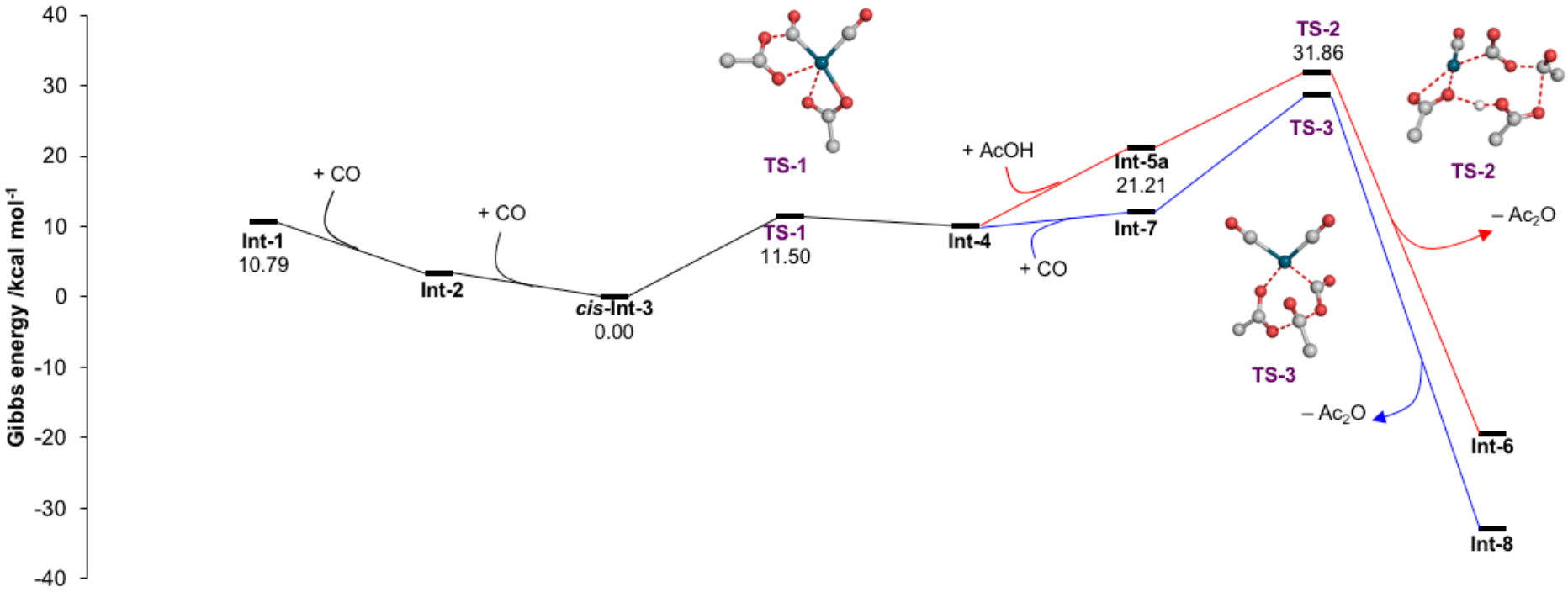


Scheme 60: Moiseev's studies on the decomposition of palladium acetate under carbon monoxide. Moiseev's proposed mechanism is indicated by dotted lines. The palladium complexes are proposed to be trimeric, however they have been drawn as monomeric species for clarity.

Despite Moiseev's extensive kinetic studies,[150] supporting evidence for the palladium intermediates invoked in this mechanism is very limited. From the reaction of palladium acetate and carbon monoxide, Moiseev did isolate a light brown residue, which was proposed to be a palladium acyl complex (**287**) due to the observation of an IR stretch at 1810 cm^{-1}.[44] Unfortunately, this residue was not further characterised by alternative analytical techniques. To support the mechanistic studies into the C–H carbonylation of aliphatic amines, we endeavoured to acquire an improved understanding of the palladium complexes that may be formed under a carbon monoxide atmosphere. However, the experimental study of palladium(II) complexes under a carbon monoxide atmosphere is notoriously challenging and often results in rapid reduction to palladium(0).[151] We therefore opted to employ DFT calculations to study Moiseev's carbon monoxide mediated decomposition of palladium acetate in an acetic acid solvent.[150]

To commence our DFT study, the sequential binding of carbon monoxide to monomeric palladium diacetate was first investigated (Figure 4). DFT calculations were performed using the Amsterdam Density Functional (ADF) 2014.09 package with a BLYP-D3 exchange correlation potential and a TZ2P basis set (see Appendix 1 for full details). Carbon monoxide binds to monomeric palladium acetate (**Int-1,** 10.79 kcal/mol) to form a monocarbonyl complex (**Int-2**, 3.33 kcal/mol), which then binds a further molecule of carbon monoxide to produce the dicarbonyl complex (***cis*-Int-3**, 0.00 kcal/mol). The binding of each carbon monoxide complex is exergonic, which is unsurprising as carbon monoxide is a strong ligand for palladium(II).[152,153] A *trans* arrangement of ligands was also considered for the dicarbonyl complex (***trans*-Int-3**, 3.21 kcal/mol), however, this was found to be higher in energy than the corresponding *cis* complex.

Intermediate ***cis*-Int-3** displays an unusual bent binding geometry of the carbonyl ligands, with Pd–C–O bond angles of 153.6°. Additionally, the distance between the acetate's oxygen and carbonyl's carbon was surprisingly short at 2.1 Å. Taken together, the Pd–C–O angles and C–O distances are suggestive of a bonding interaction between the acetate oxygen's lone pair and the π* orbital of carbon monoxide. Indeed, Bell has described a similar carboxylate/carbonyl interaction in a $Rh(CO)_2(TFA)_2$ complex.[154] However, this carboxylate/carbonyl interaction in a palladium complex is, to the best of our knowledge, previously unreported.



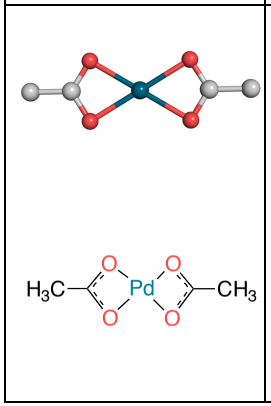
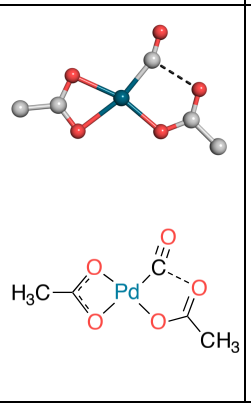
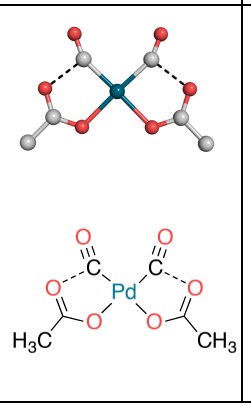
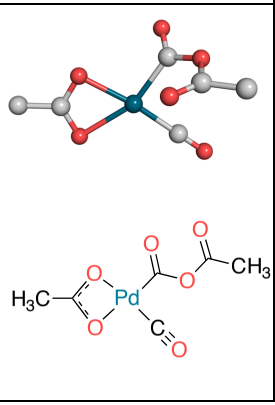
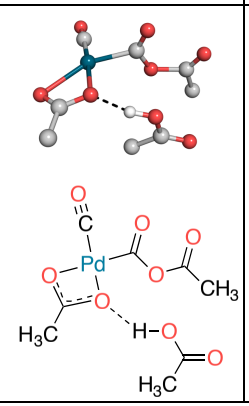
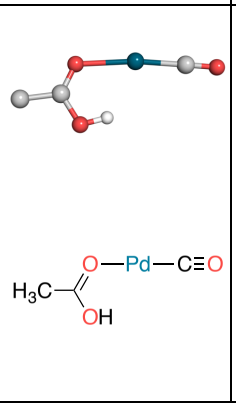
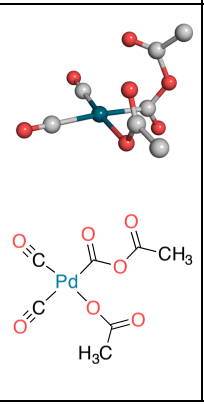
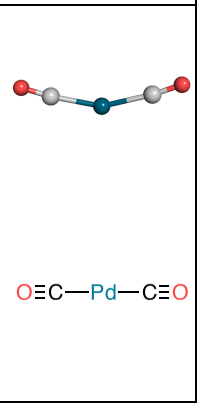
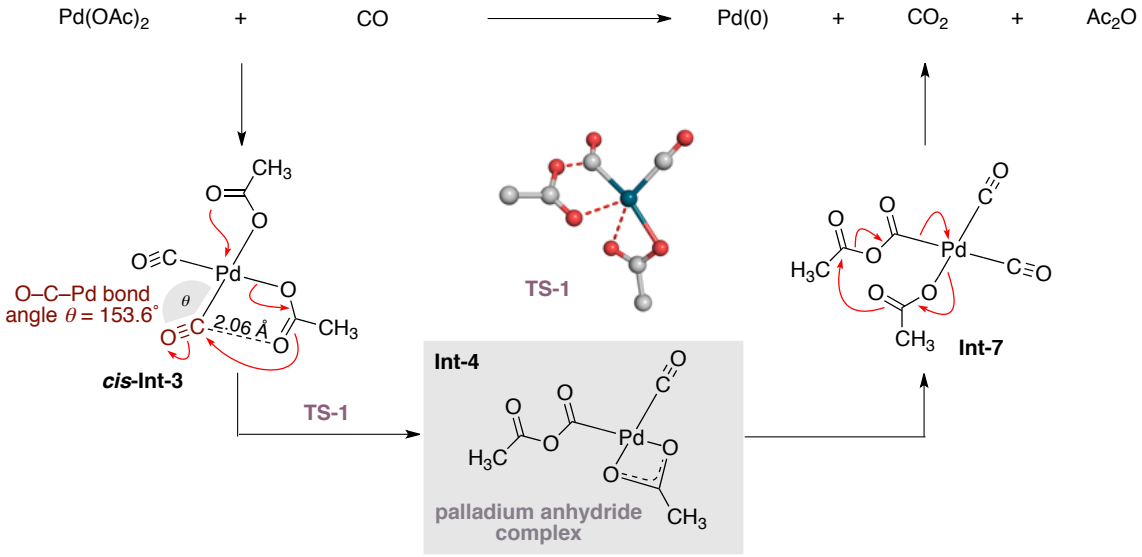
Int-1	Int-2	*cis*-Int-3	Int-4	Int-5a	Int-6	Int-7	Int-8
							

Figure 4: An energy level diagram to show the decomposition of palladium acetate mediated by carbon monoxide. The energy of ***cis*-Int-3** has been set to zero and all other energies are relative to ***cis*-Int-3**. Calculations performed using ADF 2014.05, BLYP-D3 and a TZ2P basis set using a COSMO (AcOH) solvation model at 373.15 K. Red lines show the acetic acid interception pathway, whereas blue lines illustrate the κ^1 carboxylate interception pathway.

It was proposed that the binding of one carboxylate in a κ^2 fashion might drive the migration of the other carboxylate onto the carbonyl ligand, resulting in the observed interaction becoming a σ bond. Indeed, **cis-Int-3** (0.00 kcal/mol) was found to undergo migration of a carboxylate onto a carbonyl ligand *via* **TS-1** (11.50 kcal/mol) to form a palladium anhydride complex (**Int-4,** 10.14 kcal/mol). The calculated IR frequencies for the anhydride moiety were at 1688 cm^{-1} (carbonyl proximal to palladium stretching) and 1706 cm^{-1} (carbonyl distal to palladium stretching). This suggests that the residue isolated by Moiseev (1810 cm^{-1}) is not a palladium anhydride species.[44] The possibility of CO_2 extrusion from this palladium anhydride complex (**Int-4**), as per Moissev's proposal, was then investigated by DFT calculations. However, a transition state structure for this transformation could not be found despite extensive effort, which suggests that CO_2 extrusion from the palladium anhydride complex is an unlikely process. Thus, alternative pathways that would be available from the palladium anhydride intermediate (**Int-4**) were considered.

In analogy to organic anhydrides, it was imagined that the palladium anhydride complex (**Int-4**) was an electrophilic species. As acetic acid is a nucleophile, it was speculated that acetic acid could intercept the palladium anhydride complex (**Int-4,** Figure 4). Indeed, association of acetic acid to the palladium anhydride complex (**Int-4**, 10.14 kcal/mol) afforded an adduct (**Int-5a**, 21.21 kcal/mol), from which nucleophilic attack at the carbonyl of the anhydride distal to palladium (**TS-2**, 31.86 kcal/mol) liberated carbon dioxide, acetic anhydride and a palladium(0) complex (**Int-6**, –19.43 kcal/mol). Alternative geometries for the acetic acid palladium anhydride adduct (**Int-5a**) were considered, but were found to be higher in energy (see Appendix 1 for more details).



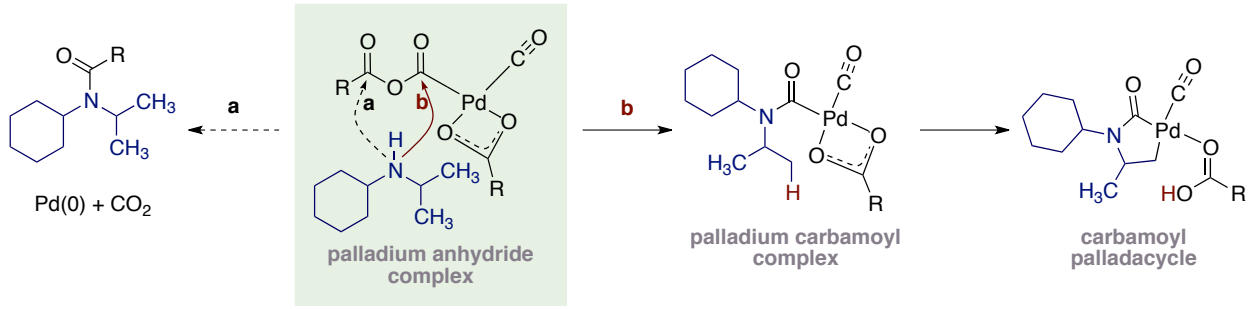
Scheme 61: A summary of the mechanism of carbon monoxide mediated decomposition of palladium acetate, as determined by DFT calculations.

In addition to acetic acid solvent acting as a nucleophile, it was recognised that palladium bound acetate could also act as a nucleophile, provided the acetate could achieve a κ^1 binding mode. Examination of this second possible reaction pathway revealed that carbon monoxide binding to palladium anhydride (**Int-4**, 10.14 kcal/mol) leads to **Int-7** (12.16 kcal/mol), which has the requisite κ^1 bound acetate. Nucleophilic attack of this κ^1 acetate on the distal carbonyl of the palladium anhydride (**TS-3**, 28.66 kcal/mol) provides a palladium(0) complex (**Int-8**, –32.92 kcal/mol), carbon dioxide and acetic anhydride. As **TS-3** (28.66 kcal/mol) is 3.20 $kcalmol^{-1}$ lower in energy than **TS-2** (31.86 kcal/mol), it is expected that

this second mechanism is the dominant pathway for palladium diacetate reduction under a carbon monoxide atmosphere. The mechanism of this reduction process is summarised in Scheme 61 and proceeds *via* a key palladium anhydride intermediate (**Int-4**). The acetic anhydride generated by this reduction process is likely to be responsible for the formation of acetamide side products in the C–H carbonylation reaction of secondary aliphatic amines.

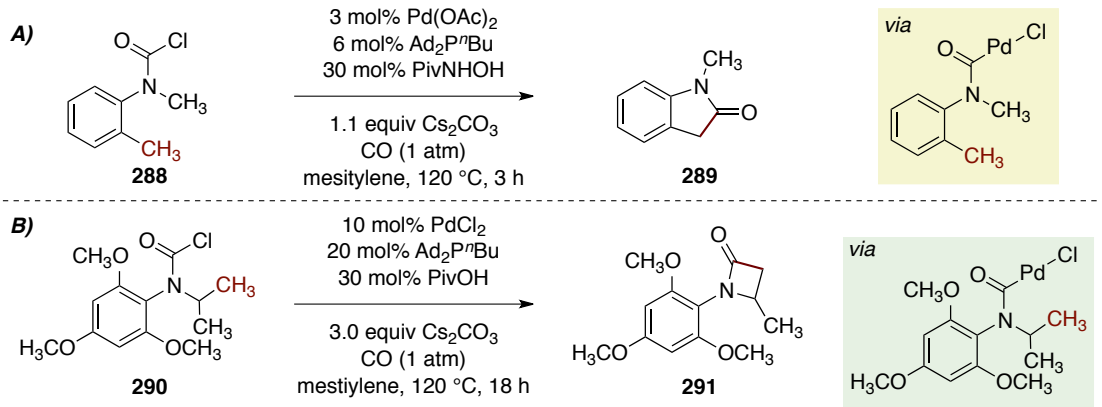
2.4.3 Palladium carbamoyl complexes as putative intermediates

Whilst considering possible mechanisms for the C–H carbonylation of aliphatic amines, it was speculated that the palladium anhydride intermediate could potentially react with aliphatic amines (Scheme 62). One possibility was that the amine could attack the carbonyl of the anhydride distal to palladium as before (Scheme 62, attack a), leading to *N*-acetylation. Alternatively, the amine could attack the carbonyl of the anhydride proximal to palladium (Scheme 62, attack b) resulting in the formation of a palladium carbamoyl complex. It was recognised that this carbamoyl complex could potentially undergo C–H activation, affording a carbamoyl palladacycle (Scheme 62), which after reductive elimination would provide a β-lactam. Thus, this 'palladium anhydride' pathway was put forward as a potential mechanism for the C(sp^3)–H carbonylation of secondary aliphatic amines.



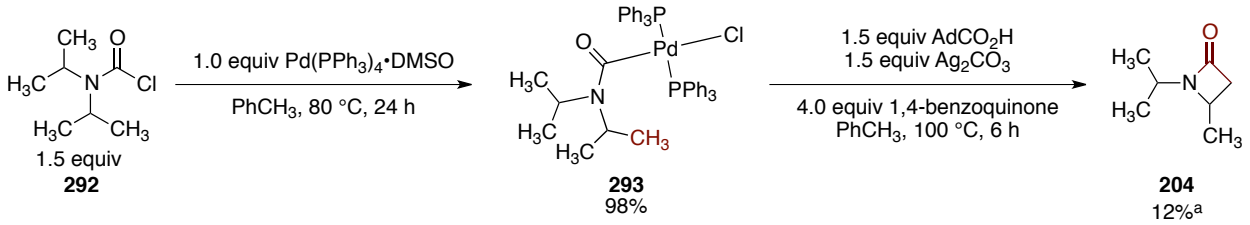
Scheme 62: Proposed amine interceptions of a palladium anhydride complex; a possible mechanism for the C–H carbonylation reaction

Precedent for C–H activation from a palladium carbamoyl complex could be found in a report by Takemoto, who reported the palladium-catalysed C–H functionalisation of carbamoyl chlorides (Scheme 63, A).[155] Shortly after the publication of the work contained in this thesis, Baudoin published a palladium-catalysed C(sp^3)–H functionalisation reaction of carbamoyl chlorides that furnished β-lactams (Scheme 63, B).[156] In both of these reactions, palladium(0) oxidatively inserts into the carbamoyl chloride to afford a palladium(II) carbamoyl complex, from which cyclopalladation can then occur.



Scheme 63: Reported examples of C–H activation from palladium carbamoyl complexes. **A)** Takemoto's C–H carbamoylation of benzylic positions; **B)** Baudoin's C–H carbamoylation of unactivated aliphatic positions.

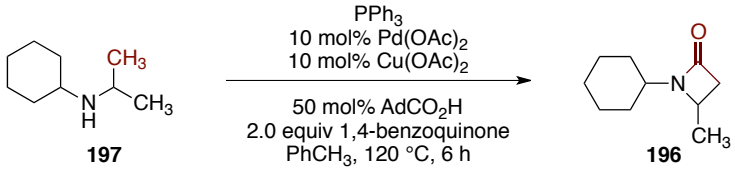
To assess the viability of carbamoyl intermediates in our C–H carbonylation of secondary aliphatic amines, carbamoyl complex **293** was synthesised by oxidative addition of *N*,*N*-diisopropylcarbamoyl chloride (**292**) to palladium *tetrakis*triphenylphosphine (Scheme 64).



Scheme 64: The synthesis and C–H carbonylation of a palladium carbamoyl complex **293**. [a] Yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

Subjecting carbamoyl complex **293** to conditions that would resemble the chemical environment of the catalytic C–H carbonylation reaction resulted in the formation of β-lactam **204**, albeit in a low yield of 12% (Scheme 64). This demonstrated that a palladium carbamoyl complex could be a viable intermediate in the catalytic C–H carbonylation reaction. It is important to note that triphenylphosphine was found to have a detrimental effect on the performance of the catalytic C–H carbonylation reaction and this may rationalise the low yield of β-lactam in the stoichiometric study (Table 5).

The successful C–H activation of carbamoyl complex **293** (Scheme 64) provided some initial supporting evidence that a 'palladium anhydride' mechanism (Scheme 62) for the C–H carbonylation of aliphatic amines was feasible. Further investigations by computation and experiment would go on to explore this mechanistic proposal in more detail.

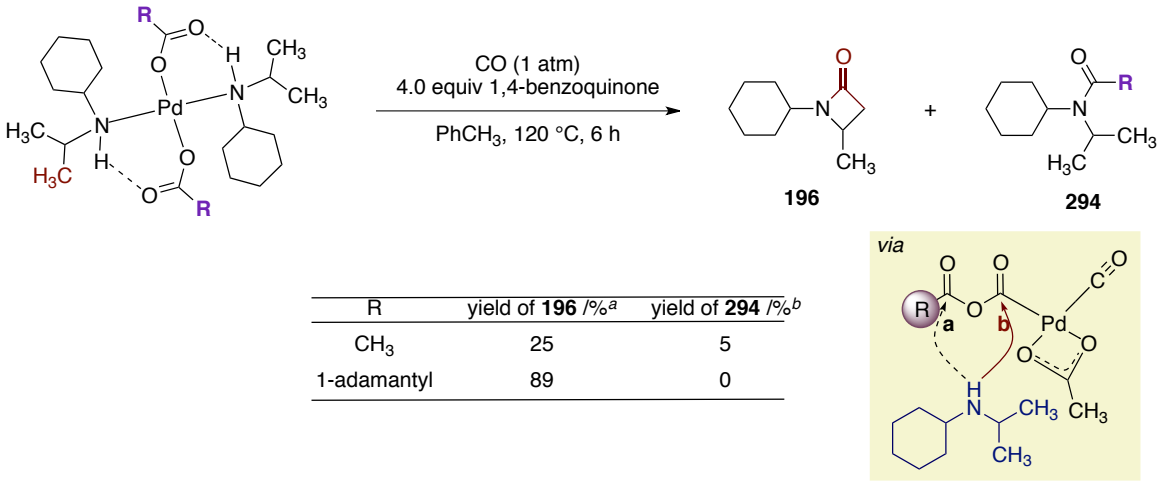


PPh_3 loading /mol%	yield of **196** /%[a]
0	65
10	40

Table 5: The effect of triphenylphosphine on the C–H carbonylation reaction, performed by Dr Darren Willcox. [a] Yield obtained by GC against a dodecane internal standard.

2.4.4 Investigating a 'palladium anhydride' mechanism

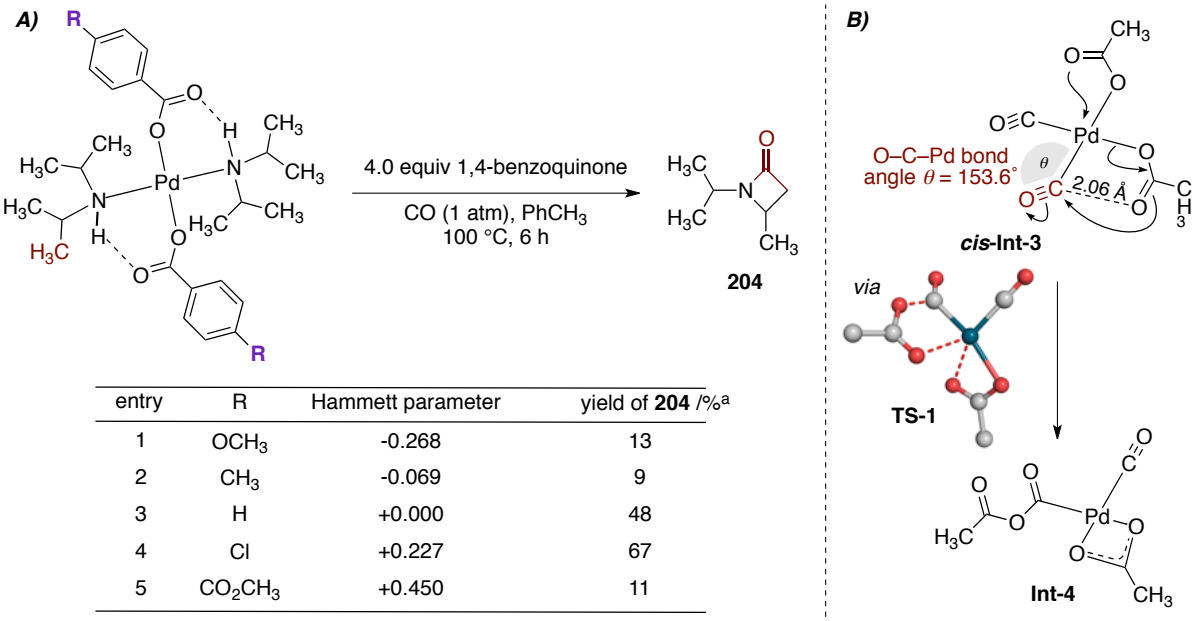
The 'palladium anhydride' mechanistic hypothesis for aliphatic amine C–H carbonylation (Scheme 62) had suggested that the nature of the carboxylate would play a critical role in determining the outcome of the reaction. Preliminary investigations had revealed that a sterically encumbered 1-adamantanecarboxylate ligand suppressed the formation of an acetamide byproduct; presumably as the generated palladium anhydride complex is less susceptible to nucleophilic attack at the distal carbonyl (*via* 'pathway a') due to increased steric hindrance (Table 6).



R	yield of **196** /%[a]	yield of **294** /%[b]
CH_3	25	5
1-adamantyl	89	0

Table 6: A steric effect of carboxylate ligands observed in the C–H carbonylation of bisamine complexes

Having established that the steric properties of carboxylate ligands were important in the C–H carbonylation reaction, we were keen to examine the effect of the electronic properties of carboxylate ligands on the C–H carbonylation reaction. It was reasoned that a series of *para* substituted benzoate ligands would allow the electronics of a carboxylate to be systematically examined, whilst having a minimal effect on steric properties. A series of bis(diisopropylamine) palladium dibenzoate complexes were prepared and subjected to C–H carbonylation conditions (Table 7, A).



entry	R	Hammett parameter	yield of **204** /%[a]
1	OCH_3	-0.268	13
2	CH_3	-0.069	9
3	H	+0.000	48
4	Cl	+0.227	67
5	CO_2CH_3	+0.450	11

Table 7: The C–H carbonylation of bisamine palladium dibenzoate complexes. **A)** The effect of benzoate electronics on the C–H carbonylation reaction. [a)] Yields obtained by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard; **B)** The transition state structure for palladium anhydride formation.

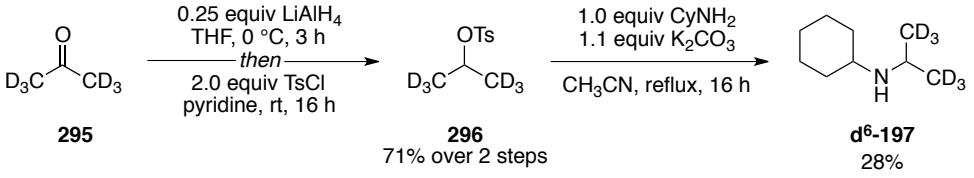
It was found that extremes of electronics on the benzoate ligands were poorly tolerated in the stoichiometric C–H carbonylation, with both methoxy (Table 7, entry 1) and ester (Table 7, entry 5) substituents giving poor results. The mildly electron withdrawing chloro substituent gave a significantly higher yield of β-lactam **204** (Table 7, entry 4) than any other examined substituent. Whilst electron poor carboxylates are commonly employed in palladium-catalysed C(sp^2)–H activations that proceed *via* an S_EAr mechanism,[50] C(sp^3)–H activations typically occur by a CMD mechanism and utilise electron rich carboxylates due to their higher basicity.[157] Unexpectedly, the C–H carbonylation of a series of

bis(diisopropylamine) palladium dibenzoate complexes had demonstrated that mildly electron poor carboxylates provided the best results.

It was clear that the electronic properties of the benzoate ligands must strongly influence another step of the C–H carbonylation mechanism, in addition to C–H activation by CMD. Studies into the carbon monoxide mediated decomposition of palladium acetate showed that the transition state structure for anhydride formation (Table 7, B, **TS-1**) involved the concerted migration of a carboxylate anion onto a neighbouring carbon monoxide ligand. This concerted carboxylate anion migration would be more facile for electron poor carboxylates, as they would better stabilise the negative charge in the transition state structure.[158–160]

In the proposed anhydride mechanism for C–H carbonylation, there are two mechanistic steps that have opposing requirements on the electronic properties of the carboxylate; C–H activation by CMD is favoured by electron rich carboxylates due to their increased basicity, whereas concerted anhydride formation is favoured by electron poor carboxylates due to increased carboxylate anion stabilisation. For an efficient C–H carbonylation reaction *via* the proposed anhydride mechanism, one would expect a balance of electronics to be required in order to facilitate both of these steps. After considering this argument, the results obtained in this study (Table 7, A) appear to be consistent with the palladium anhydride mechanism for C–H carbonylation.

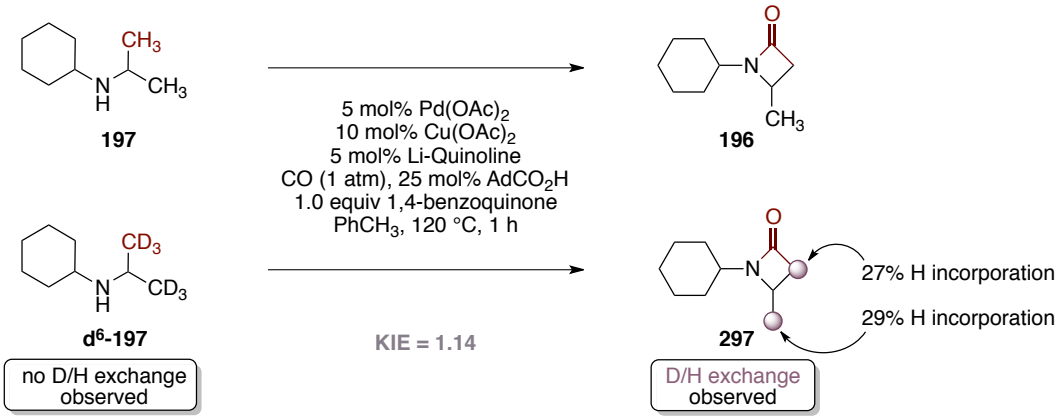
To further probe the nature of the C–H activation step, kinetic isotope effect (KIE) studies were performed. C–H activation, by definition, involves the cleavage of a C–H bond, thus important mechanistic insights can be obtained by measuring KIEs that result from differences in the rates of reaction between C–H and C–D containing substrates.[161] In order to support these KIE studies, a synthesis of d^6-*N*-cyclohexylisopropylamine (**d^6-197)** was developed (Scheme 65). The one pot reduction of d^6-acetone, followed by tosylation afforded tosylate **296** in 71% yield over two steps. Nucleophilic displacement of the tosylate by cyclohexylamine afforded **d^6-197** in 28% yield, after purification.



295 | **296** 71% over 2 steps | **d^6-197** 28%

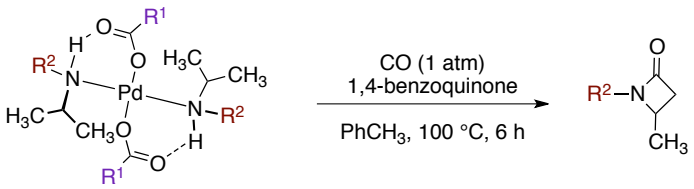
Scheme 65: The synthesis of deuterated amine **d^6-197**.

The rate constants from the C–H carbonylation of **197** and **d^6-197** were measured independently (Scheme 66) and the KIE value from parallel experiments was determined to be 1.14 (K_H/K_D). This demonstrates that C–H activation is not the turnover-limiting step of the reaction.[89] Close inspection of the C–H carbonylation of **d^6-197** by NMR revealed that hydrogen/deuterium exchange had occurred in the β-lactam product in the indicated positions (Scheme 66). It is assumed that the main proton source for this exchange is 1-adamantanecarboxylic acid. However, hydrogen/deuterium exchange was not observed in the recovered **d^6-197** starting material. Taken together, these observations indicate that C–H activation is reversible[162–164] and is preceded by an irreversible step.



Scheme 66: Kinetic isotope effect (KIE) studies. Rates of reaction determined by GC assay from parrallel experiments against a dodecane internal standard. Hydrogen incorporation was measured by ^{1}H NMR analysis of the lactam product against a 1,1,2,2-tetrachloroethane internal standard.

A number of experiments had provided us with several useful insights into the mechanism of the C–H carbonylation of aliphatic amines, nonetheless the picture of this reaction remained rather fragmented. In order to present a comprehensive mechanism for the C–H carbonylation reaction and piece together our experimental observations, DFT calculations were used to investigate the mechanism. To this end, we initially considered investigating the reaction of bis(*N*-cyclohexylisopropylamine)palladium di-1-adamantoate **274** with 1,4-benzoquinone and carbon monoxide in toluene by DFT (Table 8, entry 1). However, it was quickly realised that this system was too complex for a computational study. There are three components in this C–H carbonylation reaction, which would provide a large number of permutations for each mechanistic step that would be arduous to explore. Furthermore, bisamine **274** contained 128 atoms, which in our experience is too large for DFT studies. DFT calculations are commonly used to investigate systems of 50-100 atoms[165] and calculation times scale on the order of N^3-N^4 atoms.[166] We therefore sought to identify a bisamine complex that contained fewer atoms, but could still participate in the C–H carbonylation reaction. It had been found experimentally that the direct carbonylation of bisamine **274** could be performed in the absence of 1,4-benzoquinone to produce β-lactam **196**, albeit in a reduced yield (Table 8, entry 2). In addition, a contracted bisamine complex **298**, comprising of just 85 atoms, was competent in the C–H carbonylation reaction under 1,4-benzoquinone conditions to afford β-lactam **204** in 51% yield (Table 8, entry 3). The C–H carbonylation of **298** could be similarly performed in the absence of 1,4-benzoquinone to afford β-lactam **204** in 19% yield (Table 8, entry 4). This final reaction provided a system that worked experimentally in the laboratory, but was also simple enough to investigate computationally (Figure 5 and 6).



entry	R^1	R^2	1,4-benzoquinone equiv	yield of β-lactam /%
1	1-adamantane	Cy	4.0	89
2	1-adamantane	Cy	0.0	26
3	^{t}Bu	^{i}Pr	4.0	51
4	^{t}Bu	^{i}Pr	0.0	18

Table 8: The development of a model C–H carbonylation reaction suitable for study by DFT calculations.

Bisamine complexes, such **Int-9** are widely accepted to represent off-cycle intermediates in palladium-catalysed C–H functionalisation reactions (Figure 5).[33,167,168] In line with previous studies, we therefore anticipate that the bisamine complex (**Int-9**, 0.00 kcal/mol) undergoes a reversible dissociation of an amine ligand to provide a monoamine complex (**Int-10**, 10.63 kcal/mol). Three possible reactions of this monoamine complex were identified: carbon monoxide association (**TS-4**, 31.67 kcal/mol), β-hydride elimination (**TS-5**, 34.25 kcal/mol) and four-membered ring cyclopalladation (**TS-6**, 45.86 kcal/mol). Interestingly, the transition state structure for four-membered ring cyclopalladation (**TS-6**) was found to be 11.61 kcal/mol higher in energy than β-hydride elimination (**TS-5**). This would rationalise the inability to form a four-membered palladacycle experimentally by heating bisamine **274**, which instead resulted in β-hydride elimination (Scheme 57). Closer examination of these three transition state structures revealed that the hydrogen bond between amine and pivalate is broken in both the four-membered ring cyclopalladation (**TS-6,** O–H distance of 5.3 Å) and β-hydride elimination (**TS-5**, O–H distance of 2.5 Å) transition state structures. Conversely this hydrogen bond is maintained in the carbon monoxide association transition state structure (**TS-4**, O–H distance of 1.8 Å), which may be responsible for its relative energetic stability.

Carbon monoxide association (**TS-4**, 31.67 kcal/mol) to the monoamine complex (**Int-10**, 10.63 kcal/mol) leads to a monoamine monocarbonyl palladium dipivalate complex (***cis*-Int-11**, 5.59 kcal/mol). Although the isomeric *trans* complex (***trans*-cis-11**, 3.98 kcal/mol) was found to be lower in energy, the *cis* complex was the geometry required for further steps in the mechanism. Analogous to our previous studies (Figure 4), the carbonyl ligand of ***cis*-Int-11** had a bent geometry, with an interaction distance between carboxylate and carbonyl of 2.1 Å and a Pd–C–O angle of 154.8°, which was suggestive of a bonding interaction between the carbonyl and the carboxylate. It had previously been established that ligand association could lead to this bonding interaction becoming a σ bond, providing a palladium anhydride complex (Figure 4). A number of palladium anhydride complexes resulting from amine, carbon monoxide and κ^2 carboxylate association to ***cis*-Int-11** were considered; with those deriving from amine association found to be the lowest in energy (see Appendix 1 for more details). Therefore, the establishment of an intermolecular hydrogen bond between a free amine and **cis-Int-11** (5.59 kcal/mol) leads to **Int-12** (26.59 kcal/mol). Subsequent association of the hydrogen-bonded amine to the palladium centre drives anhydride formation by concerted carboxylate migration (**TS-8**. 30.06 kcal/mol), resulting in a palladium anhydride complex (**Int-13a**, 15.70 kcal/mol).

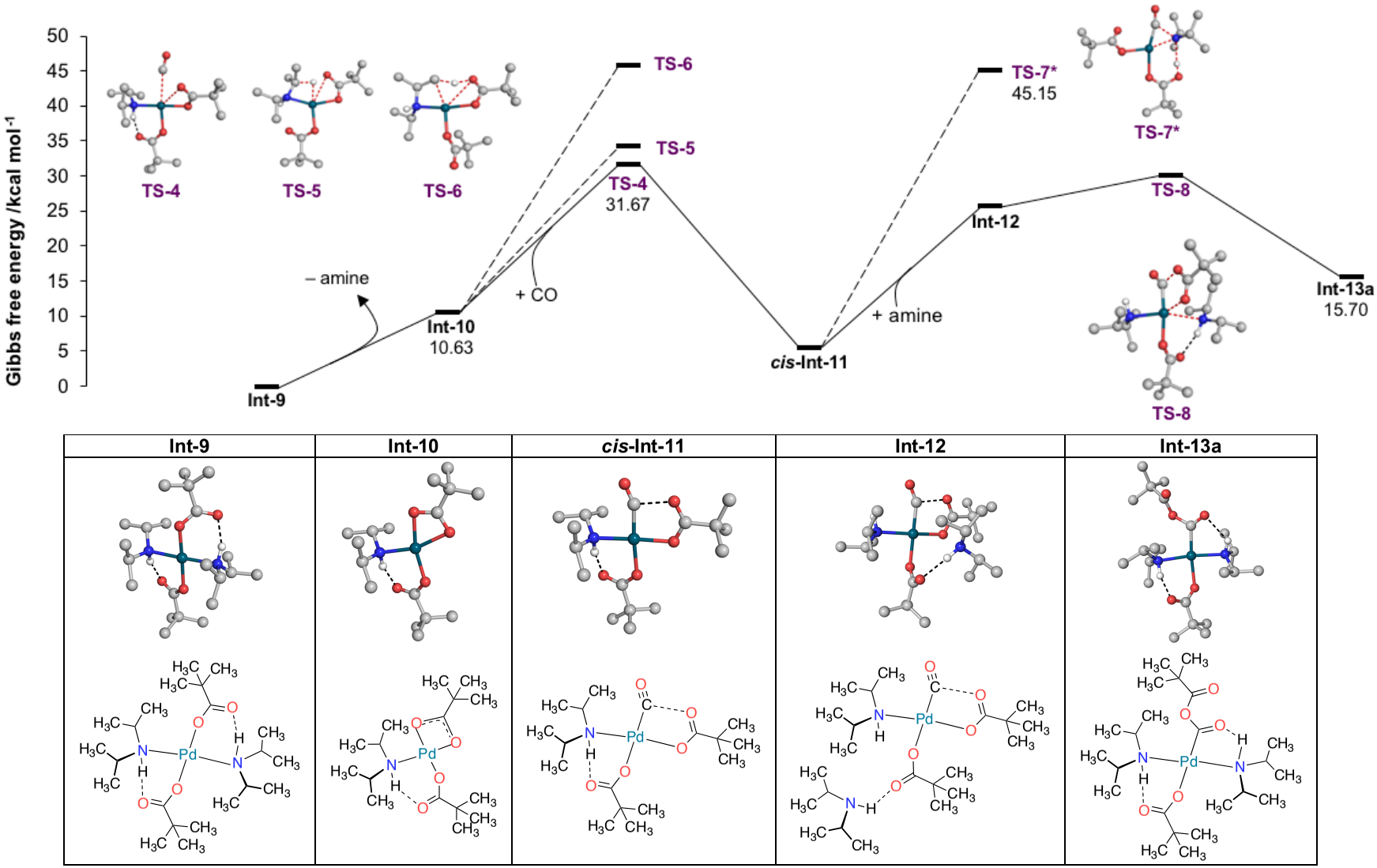
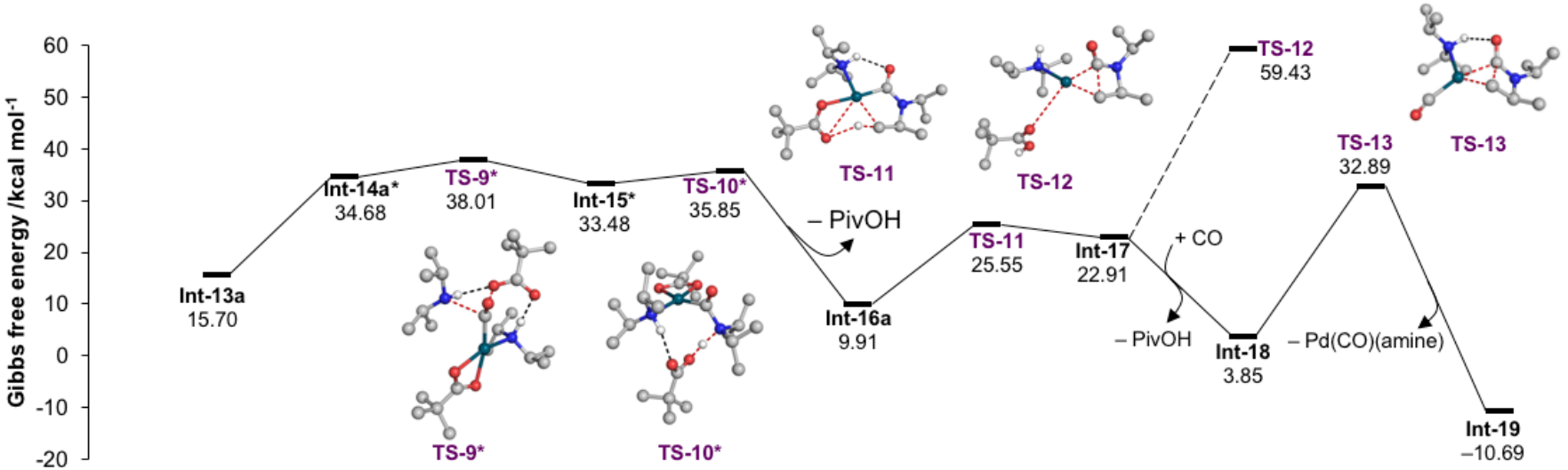


Figure 5: An energy level diagram to show the formation of a palladium anhydride intermediate (**Int-13a**) from a bisamine complex (**Int-9**). The energy of **Int-9** has been set to zero and all other energies are relative to **Int-9** Calculations performed using ADF 2014.05, BLYP-D3 and a TZ2P basis set using a COSMO ($PhCH_3$) solvation model at 393.15 K. Dotted lines indicate higher energy reaction pathways. * indicates the structure is the work of Dr Adam Smalley



Int-13a	Int-14a*	Int-15*	Int-16a	Int-17	Int-18	Int-19

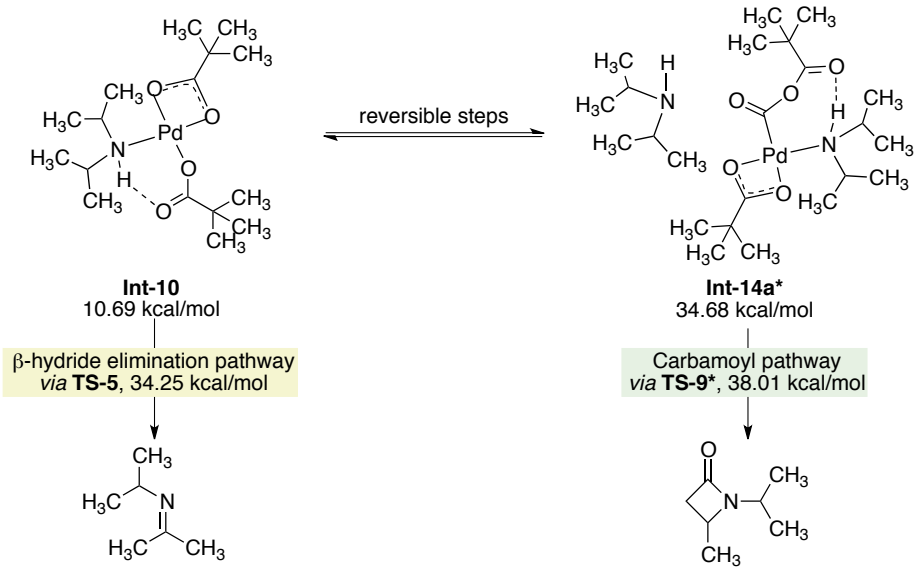
Figure 6: An energy diagram to show the formation of β-lactam (**Int-19**) from a palladium anhydride complex (**Int-13a**). The energy of **Int-9** has been set to zero and all other energies are relative to **Int-9**. Calculations performed using ADF 2014.05, BLYP-D3 and a TZ2P basis set using a COSMO ($PhCH_3$) solvation model at 393.15 K. Dotted lines indicate higher energy reaction pathways. * indicates the structure is the work of Dr Adam Smalley

DFT calculations had established a viable reaction pathway for the formation of a palladium anhydride complex (**Int-13A**); further investigations sought to explore the formation of the β-lactam product from this complex (Figure 6). Amine dissociation from bisamine palladium anhydride complex (**Int-13a**, 15.70 kcal/mol) provided a monoamine palladium anhydride complex with a dissociated amine (**Int-14a**, 34.68 kcal/mol). Nucleophilic attack of the dissociated amine on the palladium anhydride (**TS-9**, 38.01 kcal/mol) leads to a protonated carbamoyl complex (**Int-15**, 33.48), which after deprotonation (**TS-10** 35.85 kcal/mol) gave a palladium carbamoyl complex (**Int-16a**, 9.91 kcal/mol). A number of alternative transition state structures for carbamoyl formation from **Int-13A** were examined over the course of these studies, but were found to be higher in energy (see Appendix 1 for details). Additionally, an alternative reaction pathway for carbamoyl formation was examined; in the carbonylation of anilines it has been proposed that carbamoyl complexes can arise from the direct 1,1-migratory insertion of carbon monoxide into Pd–N bonds.[169] However, in this study, the 1,1-migratory insertion pathway to carbamoyl formation was found to be significantly higher in energy (Figure 5, **TS-7**, 45.15 kcal/mol) than amine interception of a palladium anhydride complex (**TS-9**, 38.01 kcal/mol).

The carbamoyl complex (**Int-16a**, 9.91 kcal/mol) had a hydrogen bond between the carbamoyl and amine ligands, which projected the methyl substituent of the carbamoyl ligand into the square plane of palladium. A transition state structure for cyclopalladation (**TS-11**, 25.55 kcal/mol) *via* a CMD mechanism was found, leading to a five-membered carbamoyl palladacycle (**Int-17**, 22.91 kcal/mol). Interestingly, a transition state structure for C–H activation could not be found from an alternative geometry of the carbamoyl complex, which lacked this hydrogen bond (**Int-16b**, see Appendix 1 for details). The closeness in energy between the carbamoyl palladacycle (**Int-17**, 22.91 kcal/mol) and the cyclopalladation transition state (**TS-11**, 25.55 kcal/mol) suggested that C–H activation is a reversible process. This is consistent with the proton/deuterium exchange that was observed in the lactam product within the KIE studies (Scheme 66). Furthermore, the large energy gap between the carbamoyl complex (**Int-16a,** 9.91 kcal/mol) and the carbamoyl formation transition state (**TS-9**, 38.01 kcal/mol) suggests that carbamoyl formation is irreversible. As carbamoyl formation precedes C–H activation, the irreversibility of this step would rationalise the absence of proton/deuterium exchange of the **d^6-197** starting material in KIE studies (Scheme 66).

To complete the C–H carbonylation reaction, a C–C reductive elimination step from the carbamoyl palladacycle (**Int-17**) was required to release the β-lactam product. However, direct C–C bond reductive elimination from the carbamoyl palladacycle (**Int-17**, 22.91 kcal/mol) was found to be unfeasibly high in energy (**TS-12**, 59.43 kcal/mol). Reductive elimination involves an increase in electron density on the palladium atom and thus it was reasoned that a π-acceptor ligand, such as carbon monoxide, could facilitate this step.[170] Accordingly, displacement of the pivalic acid ligand by carbon monoxide led to a palladacycle (**Int-18**, 3.85 kcal/mol), from which C–C bond reductive elimination (**TS-13**, 32.89 kcal/mol) was more credible, resulting in the β-lactam product (**Int-19**, –10.69 kcal/mol). Thus, reductive elimination from a carbamoyl palladacycle to afford a β-lactam is feasible, but it is sensitive to the ligands that are bound to the palladium metal.

After considering the energy profile of the C–H carbonylation reaction as a whole (Figure 5 and 6), it was recognised that the reaction is likely to be reversible between **Int-10** and **Int-14a**. It was also noted that the carbamoyl formation transition state structure (Figure 6, **TS-9**, 38.01 kcal/mol) was higher in energy than the transition state structure for β-hydride elimination from the monoamine complex (Figure 5, **TS-5**, 34.25 kcal/mol). Although β-hydride elimination is reversible for palladium alkane complexes,[171] monoamine palladium(II) complexes undergo β-hydride elimination to form iminium ions, which are then irreversibly deprotonated to furnish imines.[172–174] β-hydride elimination, therefore, represents a competing product determining pathway (Scheme 67).[175]



Scheme 67: Competitive reaction pathways examined during DFT calculations. Experimentally, β-lactam formation is observed, however DFT calculations suggest it should be completely outcompeted by the β-hydride elimination pathway.

This was concerning; if the 'palladium anhydride' mechanistic pathway is productive, the carbamoyl formation transition state structure (**TS-9**) should be lower in energy than the competing β-hydride elimination transition state structure (**TS-5**). However, this was not observed to be the case. The disparity between the observed and expected energetic ordering of **TS-5** and **TS-9** appeared to be nonsensical, which led us to consult the DFT literature.

Several reports revealed that DFT calculations often overestimate entropy in solution.[176] This overestimation of entropy affects all mechanistic steps of a reaction pathway, but association reactions (such as carbamoyl formation, **TS-9**) are disproportionally affected as the errors are compounded. Therefore, DFT calculations will often significantly overestimate the entropic penalty to association reactions.[176–178] Although, the issue of entropy overestimation in DFT calculations is widely accepted amongst the DFT community, a consensus on how to address it is yet to be reached and a number of entropy correction factors have been put forward.[176] Due to the lack of agreement on this subject, the entropy terms of Gibbs free energies throughout this thesis have been routinely left uncorrected unless otherwise specified. To investigate whether overestimation of entropy could be responsible for the seemingly nonsensical energetic ordering of **TS-5** and **TS-9**, we opted to employ the commonly and easily applied $\Delta G_{50\%}$ correction factor to these transition states. This correction involves halving the raw entropy value obtained by calculation before calculating the Gibbs free energy. Indeed, it was found that

applying this correction factor resulted in a reversal of the energetic ordering of **TS-5** and **TS-9**, such that it reflected expectation (Table 9). Importantly, the application of the $\Delta G_{50\%}$ correction factor was not found to affect the energetic ordering of other transition states in this study (see Appendix 1 for details). Accordingly, it was deemed probable that the C–H carbonylation reaction proceeded *via* a 'palladium anhydride' mechanism and that this reaction pathway was lower in energy than β-hydride elimination.

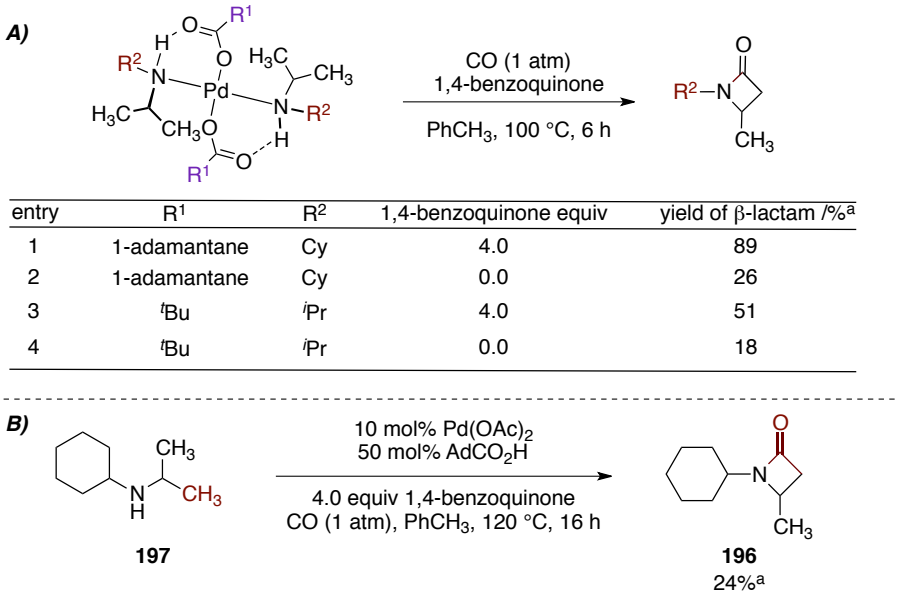
	Gibbs energy /kcalmol^{-1}	
	No entropy correction	*$\Delta G_{50\%}$ entropy correction*
TS-9 (carbamoyl formation)	38.01	29.74
TS-5 (β-hydride elimination)	34.25	43.59

Table 9: A comparison of uncorrected (ΔG) and entropy corrected ($\Delta G_{50\%}$) values for two key transition states.

In summary, DFT calculations had suggested that a 'palladium anhydride' mechanism for the C–H carbonylation of *bis*(diisopropylamine) palladium dipivalate was energetically more feasible than a traditional C–H carbonylation mechanism, involving four-membered cyclopalladation followed by carbonylation. In fact, DFT calculations suggest that β-hydride elimination outcompetes four-membered ring cyclopalladation from a mono(diisopropylamine)palladium dipivalate complex, which would mirror the formation of β-hydride elimination products observed upon heating a *bis*(N-cyclohexylisopropylamine) di-1-adamantoate complex experimentally (Scheme 57, Section 2.4.1). Furthermore, the energy profile for a 'palladium anhydride' mechanism rationalises observations made during KIE studies (Scheme 66), where proton/deuterium exchange occurred in the β-lactam product, but not in the amine starting material.

2.4.5 Investigating the role of 1,4-benzoquinone and nitrogen ligand additives

With a mechanism for the C–H carbonylation of bisamine **298** in the absence of 1,4-benzoquinone in place, attention now turned to investigating how 1,4-benzoquinone might influence steps of the mechanism. It had previously been demonstrated that 1,4-benzoquinone had a dramatic effect on the efficiency of the stoichiometric C–H carbonylation of bisamine complexes (Scheme 68, A), which suggested a mechanistic role for 1,4-benzoquinone beyond that of an oxidant.[179]



entry	R^1	R^2	1,4-benzoquinone equiv	yield of β-lactam /%[a]
1	1-adamantane	Cy	4.0	89
2	1-adamantane	Cy	0.0	26
3	^{t}Bu	^{i}Pr	4.0	51
4	^{t}Bu	^{i}Pr	0.0	18

Scheme 68: The effect of 1,4-benzoquinone on: **A)** stoichiometric C–H carbonylations of bisamine complexes; **B)** the catalytic C–H carbonylation of amine **197**. [a)] Yields determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard.

Indeed, when a catalytic C–H carbonylation of amine **197** was performed with 1,4-benzoquinone as the sole oxidant, only 2.4 turnovers were achieved, suggesting 1,4-benzoquinone is not an efficient oxidant of palladium(0) in this reaction (Scheme 68, B).

1,4-Benzoquinone is a π-acceptor ligand and has been shown to promote reductive elimination in C–H functionalisation reactions.[180,181] Inspired by these observations, we investigated the possibility of 1,4-benzoquinone facilitating reductive elimination from a carbamoyl palladacycle with DFT calculations (Figure 7). Displacement of pivalic acid from **Int-17** (22.91 kcal/mol) by 1,4-benzoquinone was found to be exergonic and led to **Int-20** (17.00 kcal/mol). Reductive elimination from this 1,4-benzoquinone ligated palladacycle (**TS-14**, 33.39) furnished a β-lactam bound to palladium(0) (**Int-21**, 10.34 kcal/mol), which after dissociation affords the free β-lactam (**Int-19**, –10.69 kcal/mol).

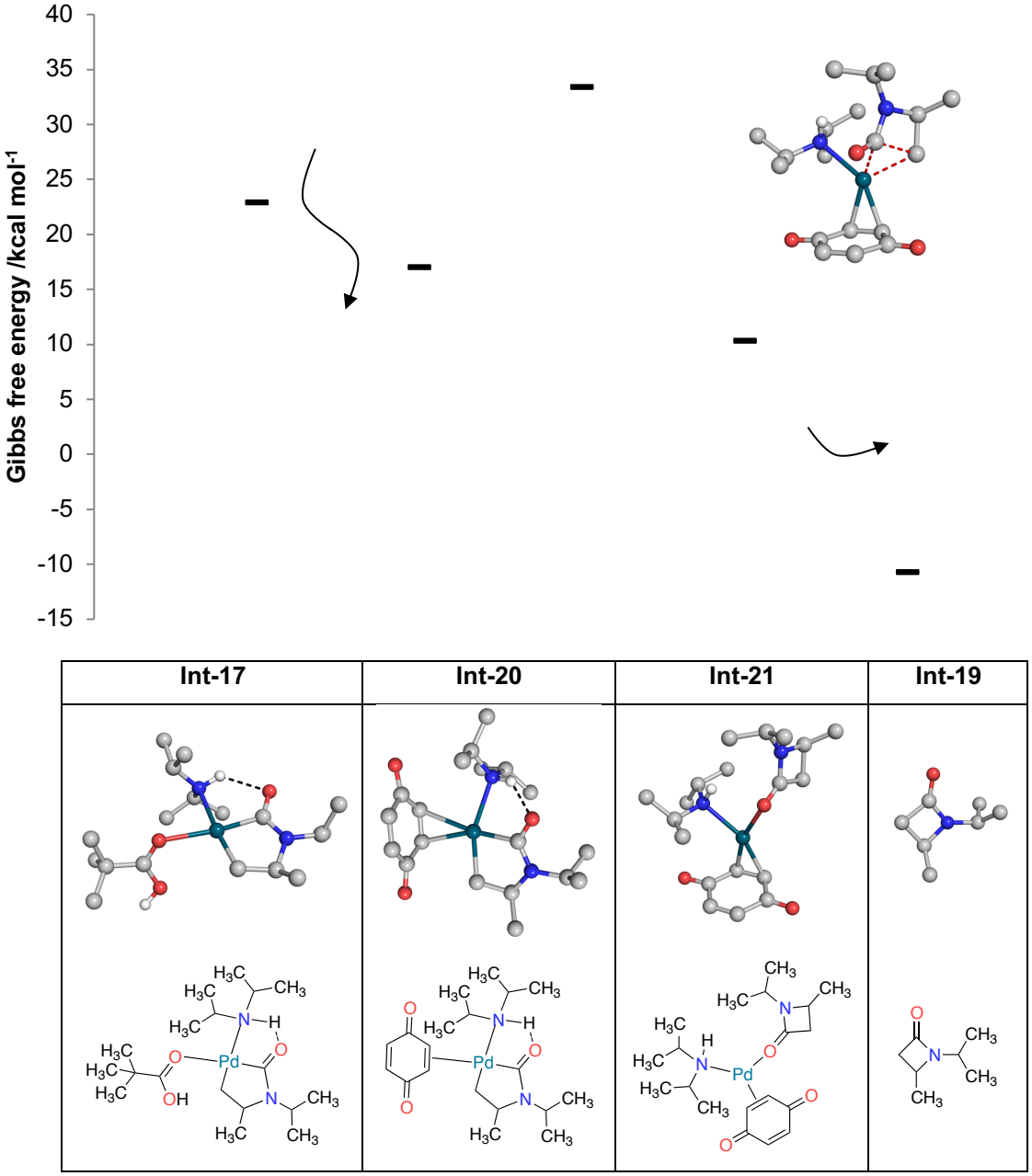
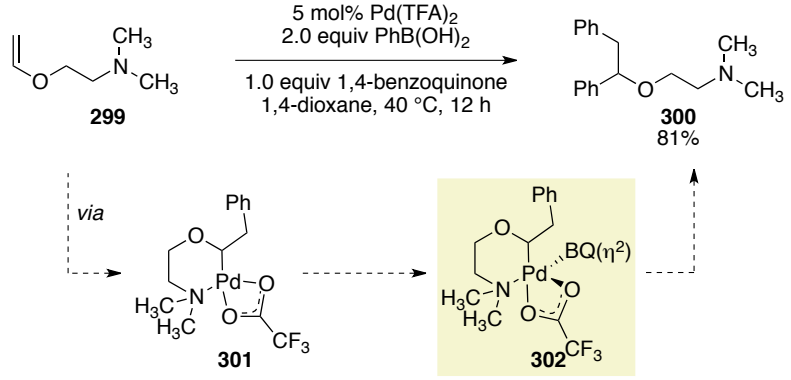


Figure 7: An energy diagram to show the 1,4-Benzoquinone mediated reductive elimination of a carbamoyl palladacycle. The energy of Int-9 has been set to zero and all other energies are relative to Int-9. Calculations performed using ADF 2014.05, BLYP-D3 and a TZ2P basis set using a COSMO ($PhCH_3$) solvation model at 393.15 K.

Intriguingly, the 1,4-benzoquinone mediated reductive elimination transition state (**TS-14**, ΔG = 33.39 kcal/mol, $\Delta G_{50\%}$ = 33.75 kcal/mol) is similar in energy to the carbon monoxide mediated reductive elimination transition state (**TS-13**, 32.89 kcal/mol, $\Delta G_{50\%}$ = 36.30 kcal/mol). Whilst this demonstrates that 1,4-benzoquinone can facilitate reductive elimination, it is not necessarily more efficient at promoting reductive elimination than carbon monoxide. However, it is important to note that the concentration of carbon monoxide in toluene is low,[45,46] whereas 1,4-benzoquinone will be present in the C–H carbonylation in significantly higher concentrations (0.1 M or 0.2 M dependent on equivalents of 1,4-benzoquinone). In the absence of 1,4-benzoquinone, it is possible that the reductive elimination step of the C–H carbonylation is challenging, due to the low concentration of carbon monoxide. It therefore seems likely that one role of 1,4-benzoquinone is to facilitate reductive elimination from **Int-17** to give β-lactam.

Whilst considering other roles that 1,4-benzoquinone may play in the carbonylation reaction, we became aware of a report from Sköld, which suggested that 1,4-benzoquinone could suppress β-hydride elimination.[182] Sköld investigated the mechanism of Larhed's palladium-catalysed diarylation of vinyl ethers (Scheme 69).[183] DFT calculations indicated that while β-hydride elimination was possible from complex **301**, association of 1,4-benzoquinone to this complex resulted in pentacoordinate complex **302**, which provided a lower energy transmetalation pathway leading to the diarylation product **300**.

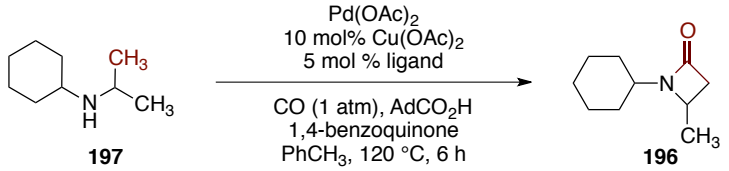


Scheme 69: Larhed's diarylation of vinyl ether **299**. Sköld proposed that 1,4-benzoquinone suppressed β-hydride elimination by forming a pentacoordinate complex **302**.

DFT calculations were conducted to examine whether 1,4-benzoquinone could behave in a similar way in our C–H carbonylation reaction and bind to monoamine complexes in order to suppress β-hydride elimination. However, optimised structures for pentacoordinate monoamine complexes could not be found and thus this possibility was considered unlikely.

To summarise, the main role of 1,4-benzoquinone appears to be to facilitate reductive elimination from the carbamoyl palladacycle. The involvement of 1,4-benzoquinone in the oxidation of palladium(0) to palladium(II) cannot be ruled out and 1,4-benzoquinone may work in concert with copper species to effect this.[184] Alone, 1,4-benzoquinone does not appear to be an efficient oxidation for palladium(0) in this C–H carbonylation reaction. 1,4-Benzoquinone does not appear to play a role in β-hydride elimination suppression, however, the possibility of 1,4-benzoquinone interacting with intermediates other than the monoamine complex cannot be ruled out at this stage.

The use of Li-quinoline and quinuclidine additives in the catalytic C–H carbonylation had allowed the loading of many components of the C–H carbonylation reaction to be substantially decreased (Table 10).

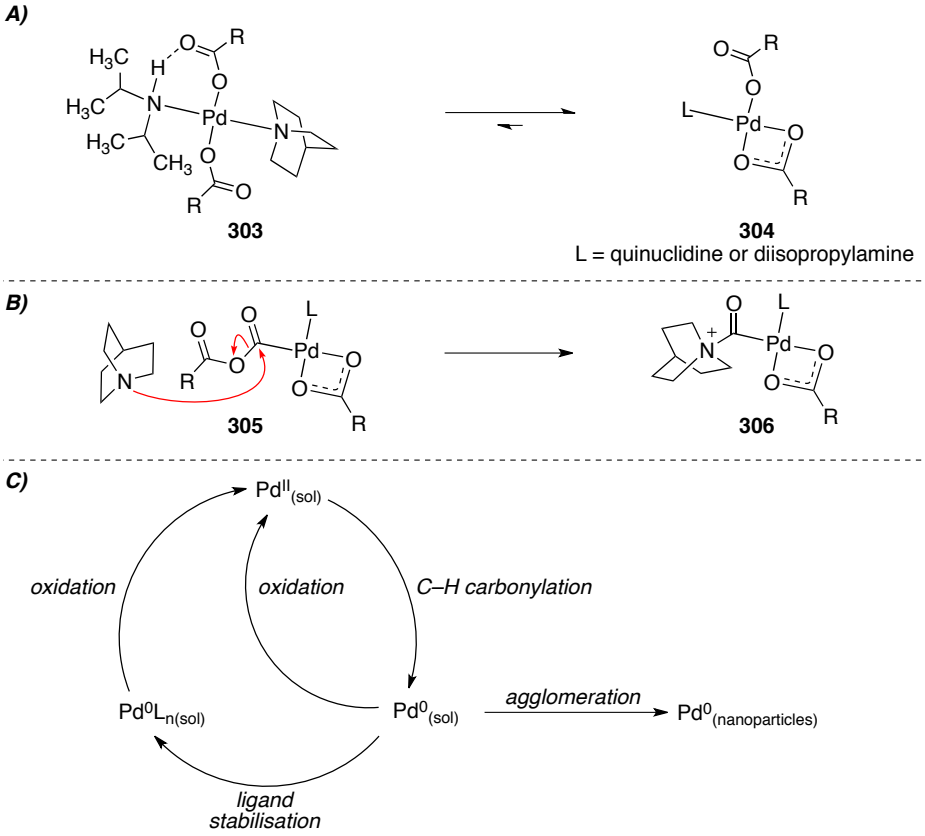


197 **196**

entry	ligand	$Pd(OAc)_2$ /mol%	$AdCO_2H$ /mol%	1,4-benzoquinone /equiv	yield of **196** /%[a]
1	none	10	50	4.0	81
2	none	5	25	1.0	56
3	Li-quinoline	5	25	1.0	83
4[b]	quinuclidine	5	25	1.0	83

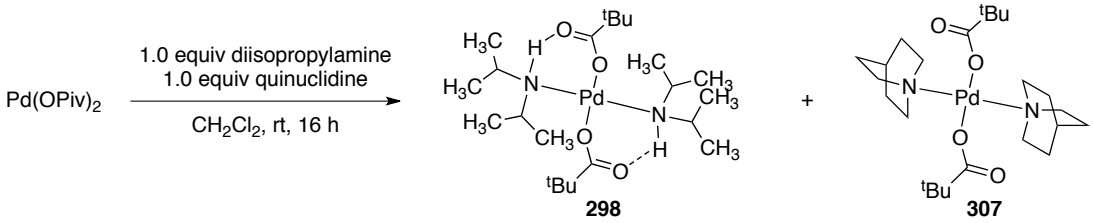
Table 10: The C–H carbonylation reaction of **197** under different reaction conditions developed during this project. [a] Yield determined by ^1H NMR against a 1,1,2,2-tetrachloroethane internal standard. [b] Reaction performed by Dr Darren Willcox.

Three proposals for the role of the nitrogen ligand additives were put forward, which were examined in turn by a combination of practical experiments and DFT calculations (Scheme 70). As Li-quinoline and quinuclidine were as equally effective in the C–H carbonylation reaction (Table 10, entries 2 and 3), we opted to study the role of quinuclidine in DFT studies, as it has fewer atoms than Li-quinoline and is thus less computationally expensive to study.



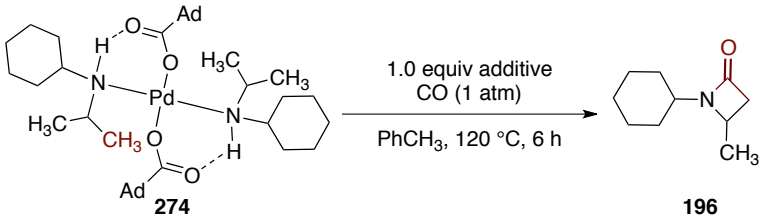
Scheme 70: Three possible roles of nitrogen ligand additives in the C–H carbonylation reaction. **A)** Facilitating ligand dissociation from mixed nitrogen ligand/amine complexes. **B)** Nucleophilic catalysts. **C)** Palladium(0) scavengers that minimise agglomeration of palladium(0).

Firstly, it was proposed that mixed amine ligand palladium complexes (**303**) could be formed under the reaction conditions (Scheme 70, A). It was imagined that ligand dissociation from these mixed complexes (**303**) could be more facile than from a bisamine complex, thus facilitating the formation of monoligand complexes (**304**) required for carbon monoxide association. To assess this proposal, palladium pivalate was subjected to equimolar quantities of quinuclidine and diisopropylamine (Scheme 71). Careful diffusion ordered spectroscopy (DOSY) NMR analysis of the resulting crude mixture revealed that only bisamine (**298**) and bisquinuclidine complexes (**307**) resulted; the mixed complex did not form. Furthermore, DFT calculations illustrated that the formation of this mixed complex was disfavoured by 19.46 kcal/mol relative to the formation of the two homocomplexes (2 × **Int-22** compared to **Int-9** and **Int-21**, see Appendix 1 for more details). Taken together, these results suggested that the formation of mixed ligand complexes in the C–H carbonylation reaction was highly improbable.



Scheme 71: Subjection of palladium pivalate to equimolar quantities of diisopropylamine and quinuclidine. Mixed ligand complexes were not observed.

Secondly, it was proposed that the nitrogen ligand additives could act as nucleophilic catalysts and intercept the palladium anhydride intermediate to provide an activated acyl complex **306** (Scheme 70, B). This activated acyl palladium electrophile **306** could then undergo nucleophilic attack by the amine substrate to provide the carbamoyl complex *via* a lower energy pathway. This proposal was inspired by the use of nucleophilic catalysts such as DMAP in the chemistry of organic anhydrides.[185] The interception of palladium anhydride by quinuclidine was thus investigated with DFT calculations. These calculations revealed that the transition state for quinuclidine interception (**TS-15**, ΔG = 43.24 kcal/mol, $\Delta G_{50\%}$ = 34.70 kcal/mol) was higher energy than the transition state for amine interception (**TS-9**, ΔG = 38.01 kcal/mol, $\Delta G_{50\%}$ = 29.74 kcal/mol), regardless of whether an entropy correction factor was applied or not.



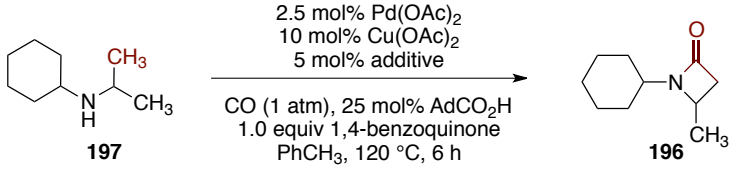
entry	additive	relative initial rate
1	diisopropylamine	5.28
2	quinuclidine	3.13
3	Li-quinoline	1.00

Table 11: Relative initial rates of the C–H carbonylation of **274** in the presence of different additives. Results obtained by Dr Darren Willcox.

Additionally, if the nitrogen ligand additives were behaving as nucleophilic catalysts, one would expect the rate of C–H carbonylation to be accelerated. When the initial rates of the stoichiometric C–H carbonylation of **274** were measured by Dr Darren Willcox, it was found that the initial rates of the C–H

carbonylation were in fact retarded by the presence of the nitrogen ligand additives (Table 11). Taken together, the DFT calculations and kinetic experiments suggest that the nitrogen ligand additives do not behave as nucleophilic catalysts in the C–H carbonylation reaction.

Thirdly, it was proposed that the nitrogen ligand additives could behave as scavengers for palladium(0) (Scheme 70, C). Palladium(0) that is generated during the C–H carbonylation reaction must be oxidised to regenerate the palladium(II) catalyst. However, the agglomeration of palladium(0) to afford palladium nanoparticles and ultimately palladium black is a competing process that results in catalyst death.[186] Palladium(0) scavengers can bind to palladium(0) forming ligated palladium species, which can be subsequently oxidised to regenerate the palladium(II) catalyst.[187] For example, Stahl has shown that pyridine can bind to palladium(0) to prevent aggregation.[188] Indeed, higher turnovers were observed when the catalytic C–H carbonylation of *N*-cyclohexylamine **197** was performed in the presence of the nitrogen ligand additives (Table 12), which is consistent with this proposal. It would thus appear that the nitrogen ligand additives can act as scavengers for palladium(0) and facilitate its oxidation.

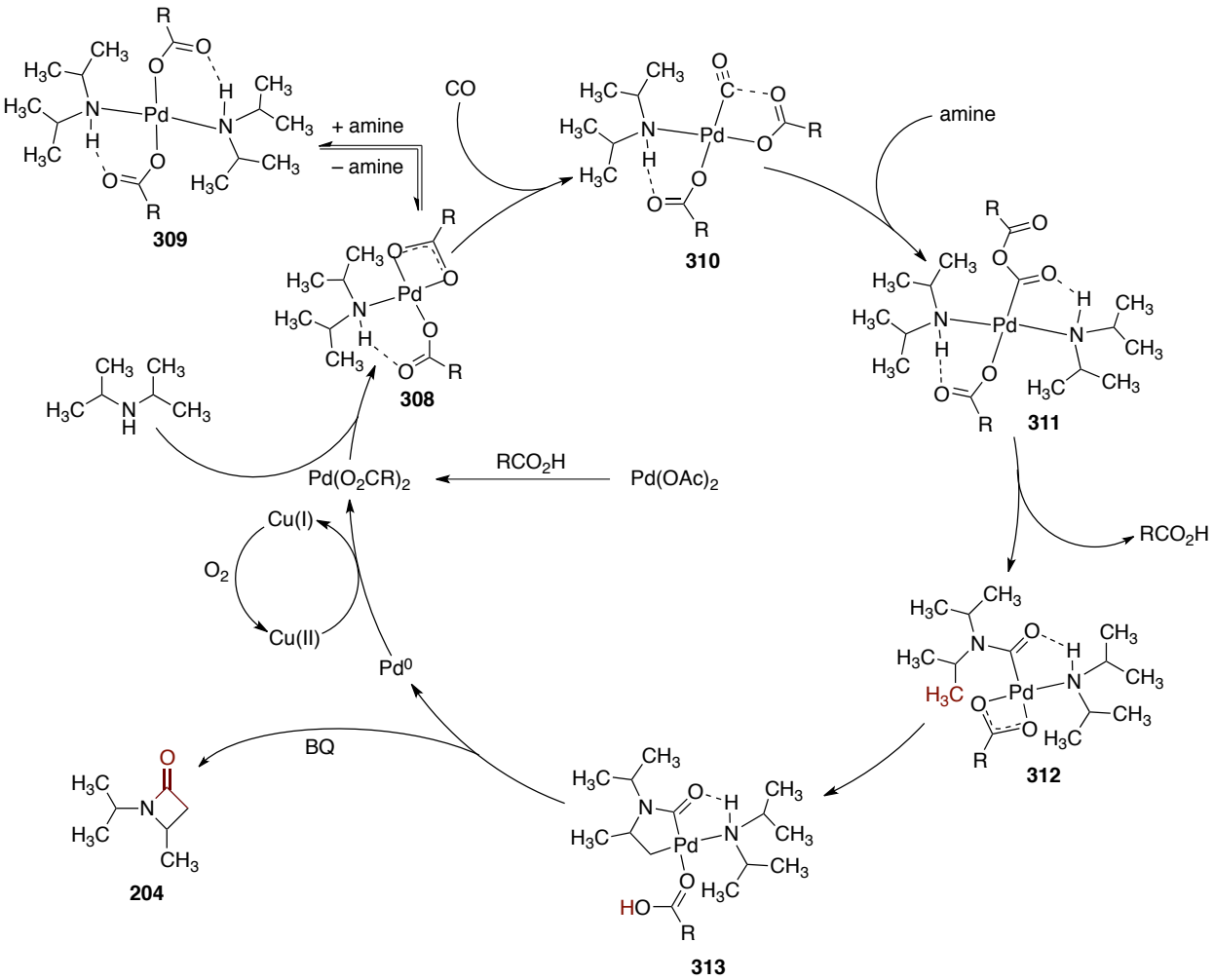


entry	additive	turnover number
1	none	14.7
2	quinuclidine	22.0
3	Li-quinoline	23.2

Table 12: The effect of nitrogen ligand additives on the turnover numbers achieved in the C–H carbonylation.

However, if the sole role of the ligands employed in the C–H carbonylation was to act as palladium(0) scavengers, one might expect a wide range of ligands to be tolerated in the reaction. Interestingly, Dr Darren Willcox's ligand optimisation studies have shown that the C–H carbonylation reaction can be remarkably sensitive to the ligand employed. The sensitivity of the reaction to ligands perhaps suggests that the nitrogen ligand additives perform additional roles within the C–H carbonylation, which are yet to be elucidated.

In summary, a combination of practical experiments and computation had suggested that the C–H carbonylation of secondary aliphatic amines proceeds *via* a novel 'palladium anhydride' mechanism (Scheme 72). Palladium dicarboxylate undergoes sequential association of amine and carbon monoxide ligands to provide monoamine monocarbonyl palladium complex **310**. Association of an amine ligand to this complex drives the migration of the carboxylate ligand onto the carbonyl ligand, leading to palladium anhydride **311**. This palladium anhydride intermediate is electrophilic and can be intercepted by an amine nucleophile leading to a palladium carbamoyl complex (**312**), from which C–H activation then occurs. The resultant palladacycle (**313**) finally undergoes reductive elimination to release a synthetically useful β-lactam product (**204**). For secondary amines bearing hydrogens on the α-carbon to the amine motif, this mechanism allows β-hydride elimination to be overcome and dramatically increases the scope of amines that are amenable to C–H carbonylation.



Scheme 72: An mechanistic overview of the C–H carbonylation of simple secondary aliphatic amines bearing hydrogens on the α-carbon to the amine motif. These amines would traditionally be expected to undergo deleterious β-hydride elimination when treated with palladium(II) catalysts.

3. Conclusions and outlook

Since Tsuji's seminal publication on the stoichiometric C–H carbonylation of azobenzene,[60] the scientific community's approach to palladium-catalysed C–H carbonylation has been remarkably consistent. Researchers have aimed to perform the C–H activation of a substrate using a palladium(II) catalyst, insert carbon monoxide into the resulting Pd–C bond and finally reductively eliminate a product. Previous work within the Gaunt group has demonstrated that this mechanism can be applied to the C–H carbonylation of highly hindered 'Type F' secondary aliphatic amines (Figure 8).[33] However, the results presented in this PhD thesis suggest that competitive β-hydride elimination prevents this mechanism from being applied to other structural classes of secondary aliphatic amine (Figure 8, 'Type A' to 'Type E').

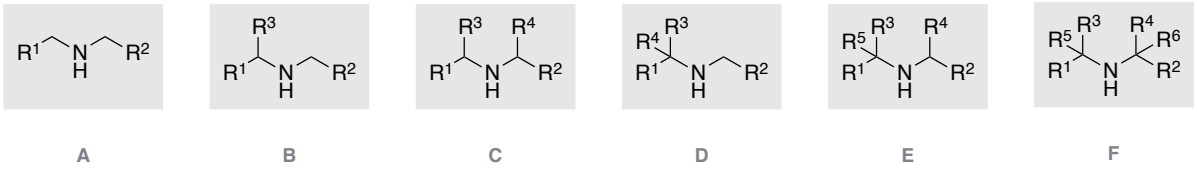
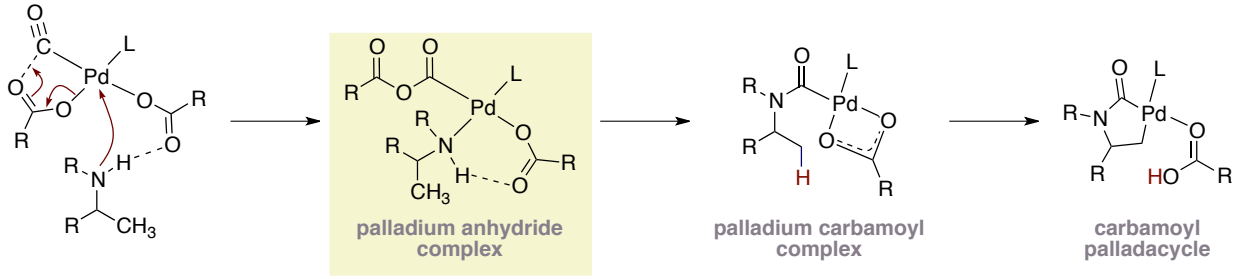


Figure 8: The structural sub-classes of secondary aliphatic amines.

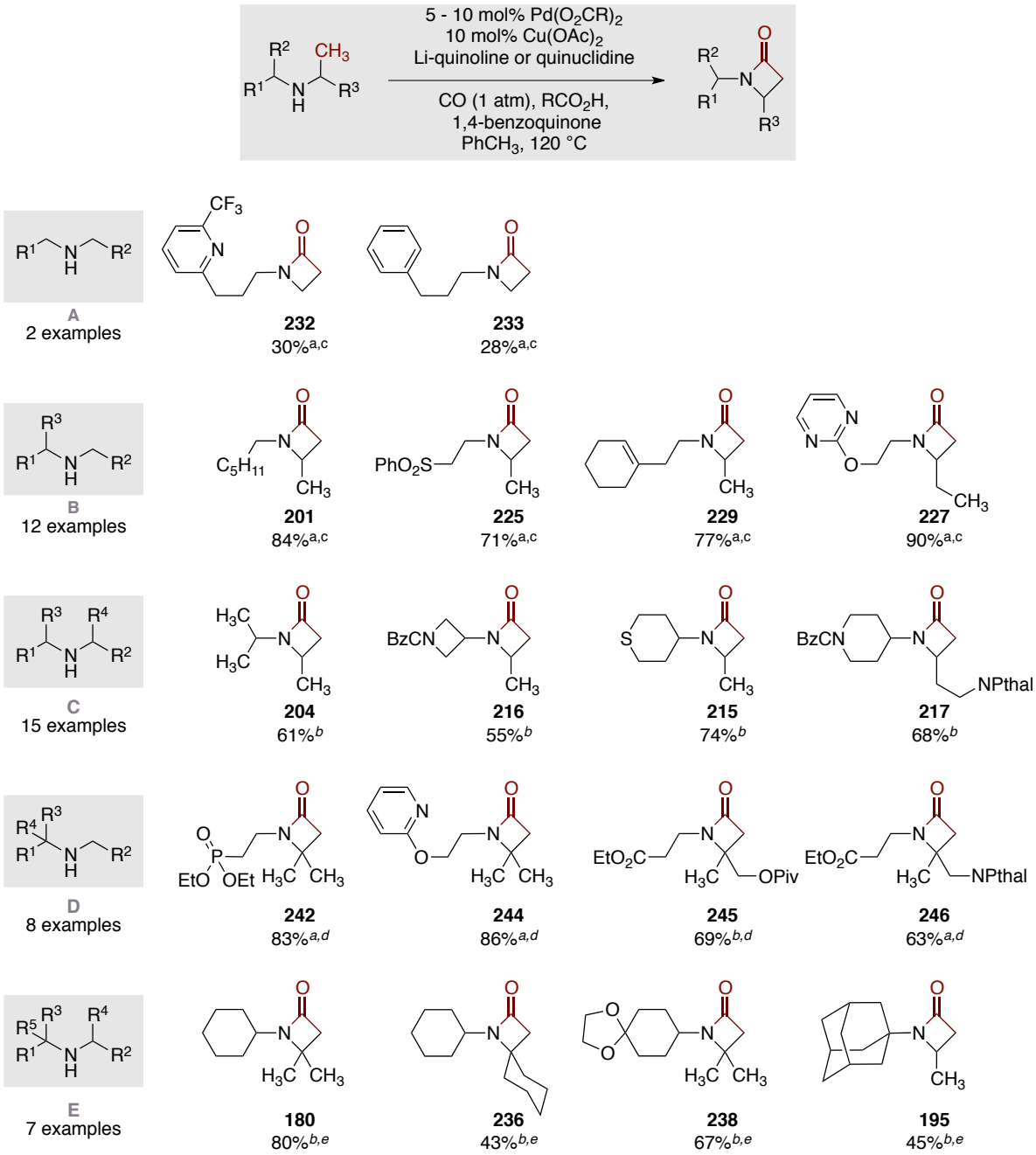
During the course of these PhD studies, a combination of experiment and DFT calculations has suggested a new mechanistic paradigm for palladium-catalysed C–H carbonylation. A previously unprecedented organometallic transformation was discovered; DFT calculations showed that a carboxylate ligand can migrate onto a neighbouring carbonyl ligand in palladium(II) complexes, providing access to palladium anhydride complexes (Scheme 73). These palladium anhydride complexes are proposed to be inherently electrophilic and readily intercepted by nucelophiles. In the case of secondary aliphatic amines, nucleophilic interception of the palladium anhydride complex provides a palladium carbamoyl complex, from which C–H activation occurs. The resulting carbamoyl palladacycle then undergoes reductive elimination to produce synthetically versatile β-lactam products.



Scheme 73: A new 'palladium anhydride' mechanism for C–H carbonylation.

In collaboration with others, C–H carbonylation conditions were established that we believe enable this new 'palladium anhydride' mechanistic pathway. Under these reaction conditions, previously intractable subclasses of secondary aliphatic amines ('Type A' to 'Type E', Figure 8) are amenable to C–H carbonylation. The reaction was illustrated on over 45 examples and accepted a wide range of functional groups. Notably, even functional groups that usually cause issues in palladium-catalysed C–H functionalisation reactions were tolerated, including heteroaromatics and thioethers (Scheme 74). The C–H carbonylation reaction could even be applied as a late-stage diversification tactic on biologically active secondary aliphatic amines, providing synthetically useful analogues. We expect the generality of the C–H carbonylation procedure will lead to its broad application among practitioners of synthetic and medicinal chemistry. Moreover, we anticipate that the postulated palladium anhydride species could be intercepted

by other nucleophiles, which may lead to opportunities to develop C–H carbonylation reactions of other aliphatic molecules. The work described in this PhD thesis was published in *Science*.



Scheme 74: A summary of the substrate scope of the C–H carbonylation of secondary aliphatic amines. [a)] 10 mol% $Pd(O_2CMes)_2$, 10 mol% $MesCO_2H$, 30 mol% quinuclidine, 2.0 equiv phenyl-1,4-benzoquinone; [b)] 10 mol% $Pd(OAc)_2$, 25 mol% $AdCO_2H$, 10 mol% Li-quinoline, 2.0 equiv 1,4-benzoquinone; [c)] reaction performed by Dr Darren Willcox; [d)] reaction performed by Kirsten Hogg; [e)] reaction performed by Dr Jonas Calleja

4. Synthesis Experimental

4.1 General considerations

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Bruker AM 400 (400 MHz) or an Avance 500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in d^1-chloroform (7.26 ppm), d^6-benzene (7.16 ppm), d^6-dimethyl sulfoxide (2.50 ppm), d^4-methanol (3.31 ppm) or d^3-acetonitrile (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants, assignment). Coupling constants are quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Bruker AM 400 (100 MHz) or an Avance 500 (126 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in d^1-chloroform (77.16 ppm), d^6-benzene (128.06 ppm), d^6-dimethylsulfoxide (39.25 ppm), d^4-methanol (49.00 ppm) or d^3-acetonitrile (1.32 ppm). DEPT135, nOe experiments and 2-dimensional experiments (COSY, HSQC and HMBC) were used to support assignments where appropriate.

High-resolution mass spectra (HRMS) were measured at the EPSRC Mass Spectrometry Service at the University of Swansea. Infrared (IR) spectra were recorded on a Perkin Elmer 1FT-IR Spectrometer fitted with an ATR sampling accessory as either solids or neat films, either through direct application or deposited in chloroform, with absorptions reported in wavenumbers (cm^{-1}).

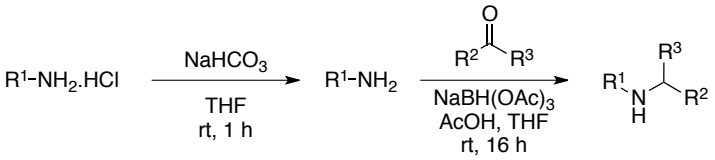
Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of nitrogen unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate. X-ray crystallography was performed on a Nonius Kappa CCD at the Cambridge University Chemistry X-Ray Laboratory.

Tetrahydrofuran, toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods. All reagents were purchased at the highest commercial quality and used without further purification. Palladium acetate trimer and copper(II) acetate were purchased from Alfa Aesar and were used without further purification. *N*- Cyclohexylisopropylamine, *N*-ethylcyclohexylamine, *N*-isopropylaniline and diisopropylamine were purchased from Sigma Aldrich and distilled over CaH_2 prior to use. 1,4-Benzoquinone was recrystallised from hexane, 1-adamantanecarboxylic acid was recrystallised from ethanol and dried *in vacuo* at 50 °C overnight. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples or gas chromatography (GC) and gas chromatography-mass spectrometry (GCMS) using a Shimadzu QP2010-SE fitted with a BPX5 column (10 m, 0.1 mm, 0.1 μm film) for FID analysis

and a SHIM-5MS column (30 m, 0.25 mm, 0.25 µm film) for MS analysis.

4.2 General procedures

General Procedure A: *One-pot reductive amination with $NaBH(OAc)_3$ and AcOH in THF*



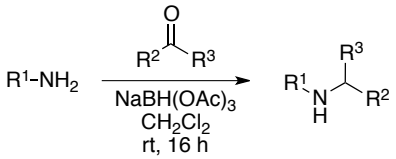
For amine.HCl salts: $NaHCO_3$ (4.20 g, 50 mmol) was added to a stirred suspension of amine hydrochloride salt (50 mmol) in THF (150 ml). The reaction mixture was stirred at rt for 1 h under nitrogen to provide an amine solution.

For free amines: Amine (50 mmol) was dissolved in THF (150 ml) to provide an amine solution.

Ketone (50 mmol) and AcOH (4.3 ml, 75 mmol) were then added to the stirred amine solution, followed by $NaBH(OAc)_3$ (12.72 g, 60 mmol). The reaction mixture was stirred for 16 h at rt under nitrogen.

The reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$ (2 × 100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide crude material.

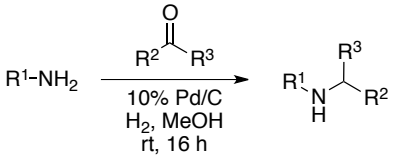
General Procedure B: *One-pot reductive amination with $NaBH(OAc)_3$ in CH_2Cl_2*



$NaBH(OAc)_3$ (5.51 g, 26 mmol) was added portionwise to a stirred solution of ketone (15 mmol) and amine (15 mmol) in CH_2Cl_2 (60 ml). The reaction mixture was stirred for 16 h at rt under nitrogen.

The reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with sat. aq. $NaHCO_3$ (2 × 50 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude material

General Procedure C: *One-pot reductive amination with Pd/C and H_2*

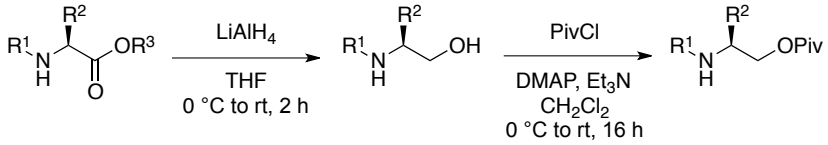


10% Pd/C (1.06 g, 1.0 mmol) was added to a stirred solution of amine (50 mmol) and ketone (50 mmol) in CH_3OH (200 ml). The reaction vessel was evacuated and backfilled with hydrogen (× 3). The reaction mixture was then stirred at rt under an atmosphere of hydrogen for 16 h.

The reaction vessel was evacuated and backfilled with nitrogen (× 3). The reaction mixture was then

filtered through Celite®, eluting with CH_3OH (50 ml) and concentrated under reduced pressure to provide the crude material.

General Procedure D: *$LiAlH_4$ reduction of amino ester, followed by pivalate protection*



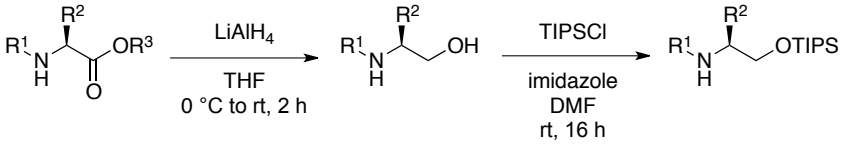
A 2.4 M solution of $LiAlH_4$ in THF (16.5 ml, 40 mmol) was added to a stirred solution of amino ester (20 mmol) in THF (100 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h under nitrogen.

The reaction mixture was quenched with H_2O (5 ml) under nitrogen, 2 M aq. NaOH (5 ml) was then added, followed by H_2O (5 ml). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (75 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with EtOAc (50 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude amino alcohol, which was used without further purification.

The amino alcohol was dissolved in CH_2Cl_2 (100 ml). Et_3N (3.4 ml, 24 mmol) and DMAP (122 mg, 1.0 mmol) were added and the reaction mixture stirred at 0 °C. Pivaloyl chloride (3.0 ml, 24 mmol) was then added dropwise at 0 °C to the stirred solution. The reaction mixture was then stirred at rt for 16 h.

The reaction mixture was washed with sat. aq. $NaHCO_3$ (50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

General Procedure E: *$LiAlH_4$ reduction of amino ester, followed by TIPS protection*



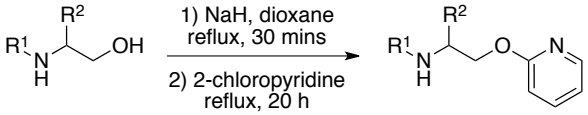
A 2.4 M solution of $LiAlH_4$ in THF (16.5 ml, 40 mmol) was added to a stirred solution of amino ester (20 mmol) in THF (100 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h under nitrogen.

The reaction mixture was quenched with H_2O (5 ml) under nitrogen, 2 M aq. NaOH (5 ml) was then added, followed by H_2O (5 ml). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (75 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with EtOAc (50 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude amino alcohol, which was used without further purification.

The amino alcohol was dissolved in DMF (20 ml). Imidazole (1.86 g, 27 mmol) followed by triisopropylsilyl chloride (5.6 ml, 26 mmol) were added to the reaction mixture and the reaction mixture was stirred at rt for 16 h.

The reaction mixture was diluted with EtOAc (200 ml), washed with sat. aq. $NaHCO_3$ (100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

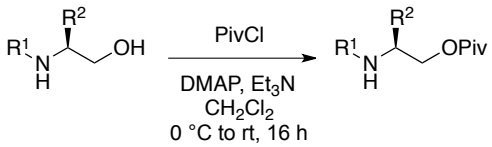
General Procedure F: *Alkoxide trapping with 2-chloropyridine*



60% NaH in mineral oil (1.20 g, 30 mmol) was added portionwise to a stirred solution of alcohol (25 mmol) in dry dioxane (60 ml) at rt under a nitrogen atmosphere. The reaction mixture was then stirred at reflux for 30 min. 2-chloropyridine (2.8 ml, 30 mmol) was then added dropwise to the reaction mixture. The reaction was then stirred at reflux for 20 h.

The reaction mixture was allowed to cool to rt and then quenched with H_2O (10 ml). The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (150 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with CH_2Cl_2 (100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

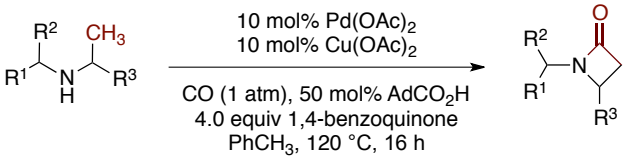
General Procedure G: *Pivaloyl protection of amino alcohol*



Pivaloyl chloride (3.7 ml, 30 mmol) was added dropwise to a stirred solution of amino alcohol (25 mmol), Et_3N (5.0 ml, 30 mmol) and DMAP (305 mg, 3.0 mmol) in CH_2Cl_2 (100 ml) at 0 °C. The reaction mixture was then stirred at rt for 16 h.

The reaction mixture was washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted by CH_2Cl_2 (2 × 100 ml), the combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

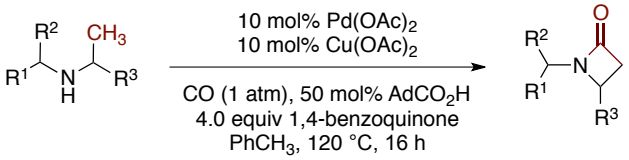
General Procedure H: *Catalytic C–H carbonylation on 0.5 mmol scale using original conditions (4.0 equivalents of 1,4-benzoquinone)*



A solution of amine (0.5 mmol) in toluene (5 ml) was added to a mixture of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), $AdCO_2H$ (45.0 mg, 0.13 mmol) and 1,4-benzoquinone (216 mg, 2.0 mmol) in a B24 50 ml round bottomed flask fitted with a 1 ¼ inch egg shaped stirrer. A B24 condenser was fitted and a new B24 Suba-Seal® placed in the top of the condenser. All joints were then carefully sealed with Teflon™ tape, followed by Parafilm. The reaction mixture was then placed under a balloon of pure CO and stirred at 300 RPM at 120 °C for 16 h unless otherwise specified, such that the solvent level in the flask was level with the oil level in the oil bath (the depth of oil in the oil bath was set to 42 mm).

The reaction mixture was then allowed to cool to rt and filtered through Celite® eluting with Et_2O (50 ml). The filtrate was concentrated and the resulting toluene solution was purified directly by flash silica column chromatography.

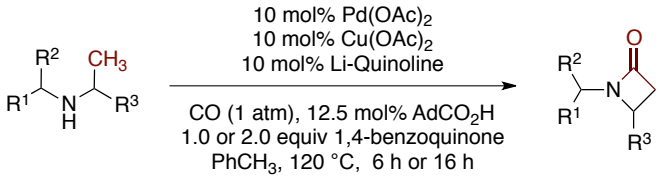
General Procedure I: *Catalytic C–H carbonylation on 5.0 mmol scale using original conditions (4.0 equivalents of 1,4-benzoquinone)*



A solution of amine (5.0 mmol) in toluene (50 ml) was added to a mixture of $Pd(OAc)_2$ (112 mg, 0.5 mmol), $Cu(OAc)_2$ (91 mg, 0.5 mmol), $AdCO_2H$ (450 mg, 1.3 mmol) and 1,4-benzoquinone (2.16 g, 20 mmol) in a B24 necked 500 ml round bottomed flask fitted with a 2 ½ inch egg shaped stirrer. A B24 condenser was fitted and a new B24 Suba-Seal® placed in the top of the condenser. All joints were then carefully sealed with Teflon™ tape, followed by Parafilm. The reaction mixture was then placed under a balloon of pure CO and stirred at 225 RPM at 120 °C for 16 h unless otherwise specified, such that the solvent level in the flask was level with the oil level in the oil bath (the depth of oil in the oil bath was set to 42 mm).

The reaction mixture was then allowed to cool to rt and filtered through Celite® eluting with Et_2O (100 ml). The filtrate was concentrated to remove Et_2O and the resulting toluene solution was purified directly by flash silica column chromatography.

General Procedure J: *Catalytic C–H carbonylation on 0.5 mmol scale using improved conditions (with Li-quinoline)*

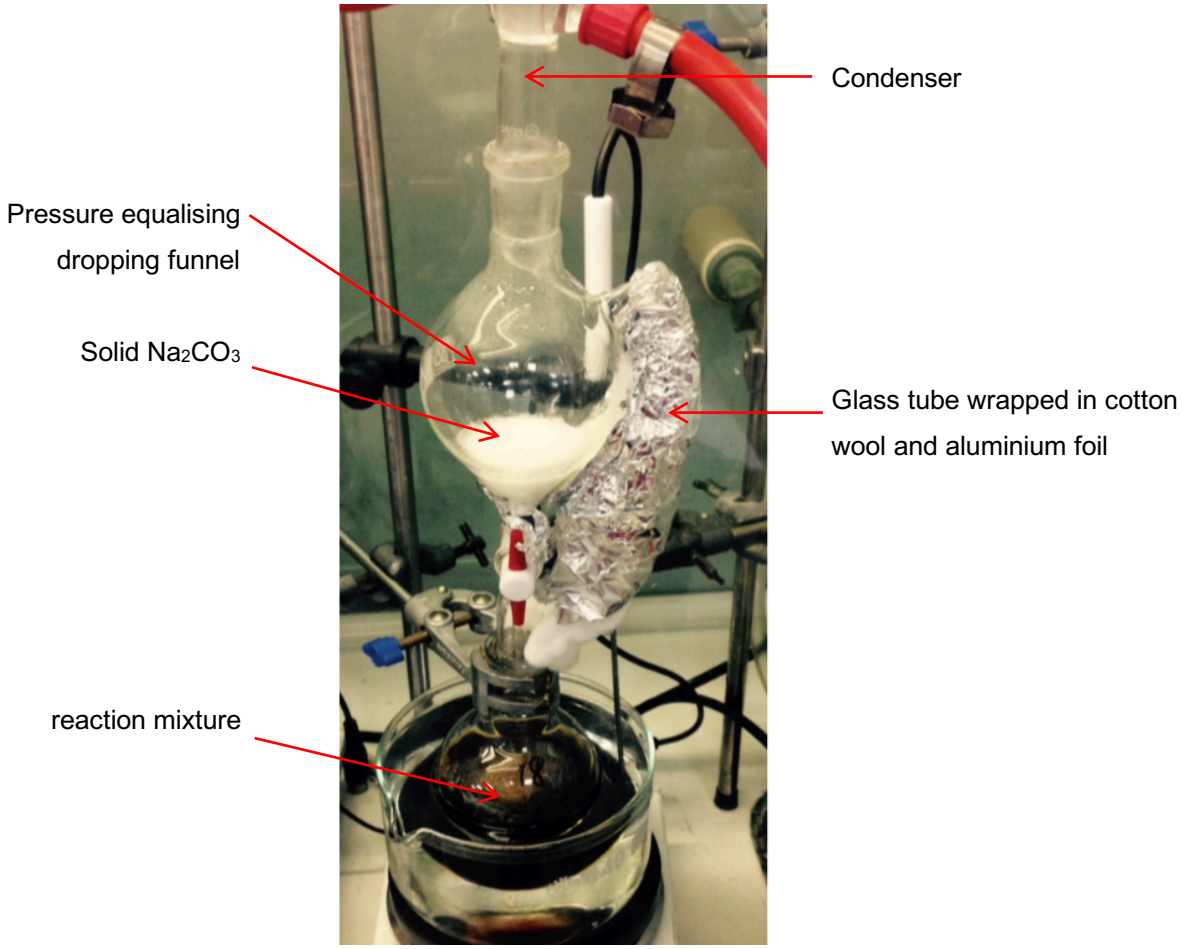


A solution of amine (0.5 mmol) in toluene (5 ml) was added to a mixture of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), Li-quinoline (10.6 mg, 0.05 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), $AdCO_2H$ (22.5 mg, 0.13 mmol) and 1,4-benzoquinone (54 mg or 108 mg, 0.5 mmol or 1.0 mmol) in a B24 necked 50 ml round bottomed

flask. A B24 condenser was fitted and a new B24 Suba-Seal® placed in the top of the condenser. All joints were then carefully sealed with Teflon™ tape, followed by Parafilm. The reaction vessel was evacuated, then backfilled with 6.25% CO in air (× 3). The reaction mixture was then placed under a balloon of pure CO and stirred at 300 RPM at 120 °C for 6 h or 16 h (dependent upon the substrate), such that the solvent level in the flask was level with the oil level in the oil bath (the depth of oil in the oil bath was set to 42 mm).

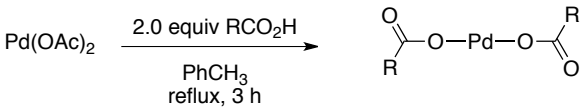
The reaction mixture was then allowed to cool to rt and filtered through Celite® eluting with Et_2O (50 ml). The filtrate was concentrated to remove Et_2O and the resulting toluene solution was purified directly by flash silica column chromatography.

Note: For selected substrates, the reaction was performed using 5 mol% $Pd(OAc)_2$ and 5 mol% Li-quinoline.



Photograph 1: A photograph to show the 'Soxhlet like set up' used in General Procedure K.

General Procedure K: *Preparation of palladium dicarboxylate complexes*

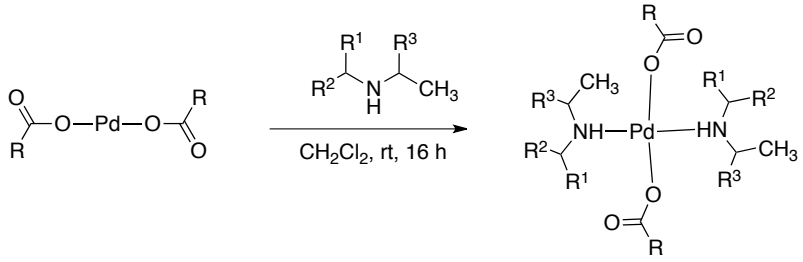


A Soxhlet like set up was used (Photograph 1), in which the round bottomed flask was charged with a solution of of $Pd(OAc)_2$ (673.5 mg, 3.0 mmol) and carboxylic acid (6.0 mmol) in toluene (50 ml) and the

Soxhlet thimble was charged with solid Na_2CO_3 (approx. 5 g). The reaction mixture was heated to reflux for 3 h, such that condensed solvent passed through the solid Na_2CO_3 (removing AcOH from the solvent) before returning to the round bottomed flask. For clarification purposes, the reaction set up has been illustrated above.

The reaction mixture was allowed to cool to rt, filtered through Celite® eluting with toluene (20 ml) and concentrated under reduced pressure to provide the crude palladium dicarboxylate.

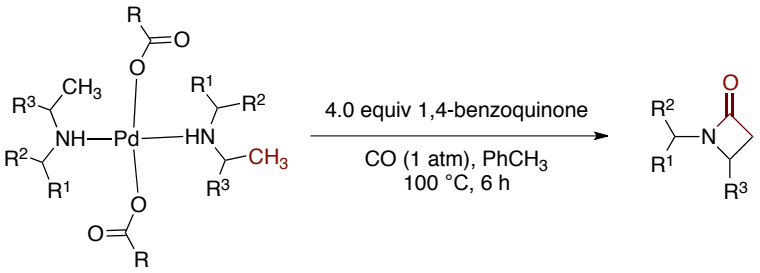
General Procedure L: *Preparation of bisamine palladium dicarboxylate complexes*



Amine (2.0 mmol) was added to a stirred solution of palladium dicarboxylate (1.0 mmol) in CH_2Cl_2 (50 ml). The reaction mixture was stirred at rt for 16 h.

The reaction mixture was filtered through Celite® eluting with CH_2Cl_2 (20 ml) and concentrated under reduced pressure to provide the crude bisamine palladium dicarboxylate complex.

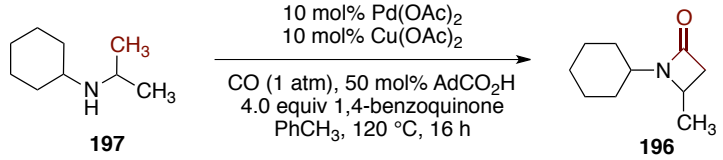
General Procedure M: *Stoichiometric C–H carbonylation of bisamine palladium dicarboxylate complexes*



Toluene (5 ml) was added to palladium complex (0.25 mmol) and 1,4-benzoquinone (108.1 mg, 1.0 mmol) in a B24 necked 50 ml round bottomed flask. A B24 condenser was fitted and a new B24 Suba-Seal® placed in the top of the condenser. All joints were then carefully sealed with Teflon™ tape, followed by Parafilm. The reaction mixture was then placed under a balloon of pure CO and stirred at 300 RPM at 100 °C for 6 h.

The reaction mixture was allowed to cool to rt, filtered through Celite® and washed through with Et_2O (30 ml). The reaction mixture was concentrated, diluted with $CDCl_3$ (approx. 1 ml) and 1,1,2,2-tetrachloroethane (25.6 µL, 0.25 mmol) added. After thorough mixing with a pipette, a ^1H NMR was acquired and the ^1H NMR yield of β-lactam was determined. Reported results are the average of 2 repeats.

4.3 Establishing a robust C–H carbonylation protocol

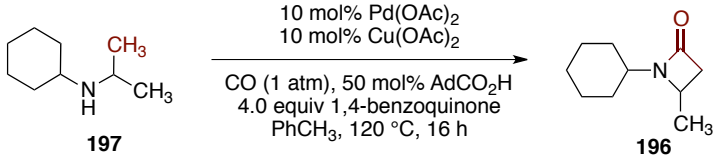


entry	BQ recrystallised from	storage of BQ	yield of **196**%[a]
1[b]	none	rt	74
2[b]	none	rt	70
3[b]	hexane	used immediately	81
4	hexane	used immediately	78
5	hexane	stored in freezer for 7 days	32
6[b]	hexane	stored in freezer for 7 days	36
7	hexane	used immediately	81
8[b]	hexane	used immediately	66
9	hexane	used immediately	62
10	hexane	used immediately	75
11	hexane	rt for 4 days	80
12	hexane	rt for 4 days	60
13	hexane	rt for 4 days	79

Table 13: Effect of 1,4-benzoquinone purity and storage on the C–H carbonylation of *N*-cyclohexylisopropylamine. Reactions were performed on a 0.3 mmol scale in 24 mm × 150 mm boiling tubes fitted with a 15 mm cylindrical stir bar. [a)] Yields were obtained by GC against an internal 1,1,2,2-tetrachloroethane internal standard; [b)] Reaction performed by Dr Darren Willcox

entry	stirring rate /RPM	scale /mmol	reaction vessel	stir bar	yield of **196** /%[a]
1	300	0.3	24 x 150 mm tube	15 mm cylindrical	62
2	300	0.3	24 x 150 mm tube	15 mm cylindrical	60
3	300	0.3	24 x 150 mm tube	15 mm cylindrical	80
4	400	0.3	24 x 150 mm tube	15 mm cylindrical	66
5	400	0.3	24 x 150 mm tube	15 mm cylindrical	69
6	400	0.3	24 x 150 mm tube	15 mm cylindrical	75
7	400	0.5	24 x 150 mm tube	15 mm cylindrical	34
8	400	0.5	24 x 150 mm tube	15 mm cylindrical	27
9	300	0.5	25 ml B14 RBF with condenser	15 mm cylindrical	62
10	300	0.5	25 ml B14 RBF with condenser	15 mm cylindrical	76
11	300	0.5	50 ml B24 RBF with condenser	45 mm cylindrical	21
12	300	0.5	50 ml B24 RBF with condenser	1 $^1/_4$ inch egg shaped	77
13	300	0.5	50 ml B24 RBF with condenser	1 $^1/_4$ inch egg shaped	76
14	300	0.5	50 ml B24 RBF with condenser	1 $^1/_4$ inch egg shaped	78

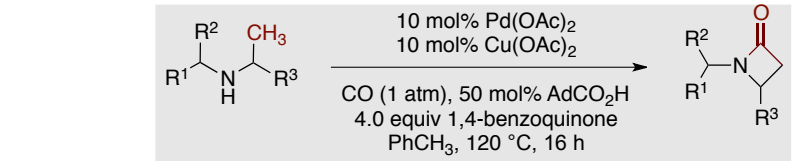
Table 14: Effect of reaction set up on the C–H carbonylation of *N*-cyclohexylisopropylamine. All reactions were positioned in the centre of the oil bath. The oil depth in the oil bath was set to 42 mm and the reaction vessel positioned such that the solvent level was equal to the oil level. Yields were determined by GC assay against an internal 1,1,2,2-tetrachloroethane standard.

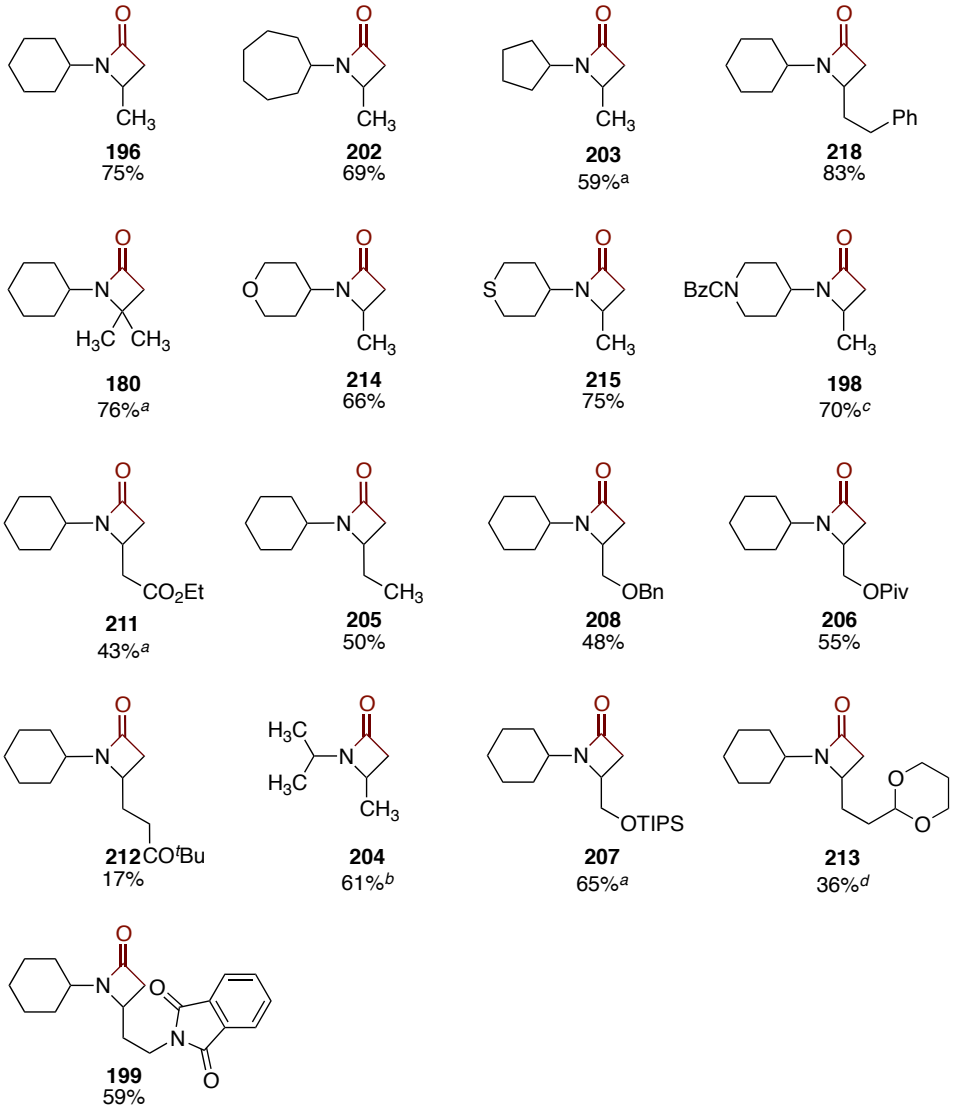


entry	scale /mmol	stirring rate /RPM	reaction vessel[a]	stir bar	yield of **196** /%[b]
1	1.0	300	100 ml B24 RBF	1 1/4 inch egg shaped	64
2	1.0	300	100 ml B24 RBF	1 1/2 inch egg shaped	58
3	1.0	300	100 ml B24 RBF	1 5/8 inch egg shaped	56
4	1.0	200	100 ml B24 RBF	2 inch egg shaped	-[c]
5	1.0	300	100 ml B24 RBF	2 inch egg shaped	-[c]
6	1.0	200	250 ml B24 RBF	2 inch egg shaped	-[c]
7	5.0	300	250 ml B24 RBF	1 1/4 inch egg shaped	52
8	5.0	300	500 ml B24 RBF	2 inch egg shaped	-[c]
9	5.0	225	500 ml B24 RBF	2 inch egg shaped	77

Table 15: Investigations towards a larger scale C–H carbonylation. All reactions were positioned in the centre of the oil bath. The oil depth in the oil bath was set to 42 mm and the reaction vessel positioned such that the solvent level was equal to the oil level; [a)] All round bottomed flasks were equipped with a B24 condenser; [b)] Yields were determined by GC assay against an internal 1,1,2,2-tetrachloroethane standard; [c)] erratic stirring meant that the reaction was abandoned

4.4 'Initial' substrate scope

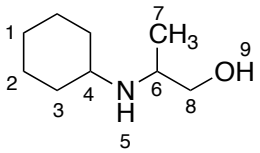




Scheme 75: The scope of the C–H carbonylation of secondary aliphatic amines under the initially developed conditions. [a)] Reaction performed by Dr Darren Willcox; [b)] Reaction performed at 100 °C; [c)] Reaction performed for 24 h; [d)] 2.0 equivalents of Li_2CO_3 were added to the reaction.

4.5 Preparation of synthetic intermediates

2-(Cyclohexylamino)propan-1-ol (**320**)



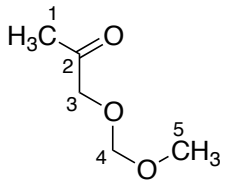
Crude material prepared according to *General Procedure C* using alaninol (8.0 ml, 100 mmol) and cyclohexanone (11.4 ml, 110 mmol)

The crude product was purified by flash silica column chromatography eluting with 1% triethylamine, 10% CH_3OH in CH_2Cl_2 to provide 2-(cyclohexylamino)propan-1-ol (14.96 g, 94 mmol, 94%) as a colourless, clear liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.08; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.52 (1H, dd, *J* = 10.3, 4.3, H_8), 3.14 (1H, dd, *J* = 10.3, 7.3, H_8), 2.87 (1H, app. qnd, *J* = 6.4, 4.3, H_6), 2.51 (1H, tt, *J* = 10.5, 4.0, H_4), 1.90 – 1.86 (2H, m, H_3), 1.75 – 1.68 (2H, m, H_2), 1.62 – 1.57 (1H, m, H_1), 1.32 – 0.96 (5H, m, H_1, H_2 & H_3), 1.02 (3H, d, *J* = 6.4, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 65.9 (C_8), 53.7 (C_4), 50.9 (C_6), 34.8 (C_3), 33.9 (C_3), 26.1 (C_1), 25.2 (C_2), 24.9 (C_2), 18.1 (C_7); **IR** ν_{max}/cm^{-1} (neat): 3274 (br O-H stretch), 2972, 2902, 1450, 1407, 13994, 1381, 1250, 1057; **HRMS** (NSI): calcd. for $C_9H_{20}ON^+$: 158.1539, found 158.1535, Δ 2.8 ppm

The observed characterisation data were consistent with literature values.[190]

1-(Methoxymethoxy)propan-2-one (**321**)



Chloromethyl ether (5.75 ml, 75 mmol) was added dropwise to a stirred solution of hydroxyacetone (3.70 g, 50 mmol) and *N*,*N*-diisopropylethylamine (17.4 ml, 100 mmol) in CH_2Cl_2 (100 ml) at 0 °C. The reaction mixture was then stirred for 16 h at rt.

The reaction mixture was then diluted with CH_2Cl_2 (100 ml), washed with sat. aq. $NaHCO_3$ (50 ml) and brine (50 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

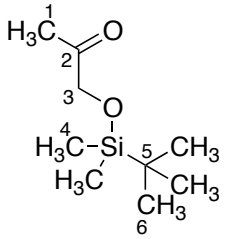
The crude product was purified by Kugelrohr distillation (b.p. ≈ 100 °C, 7 mbar) to provide 1-(methoxymethoxy)propan-2-one (2.10 g, 18 mmol, 36%) as a colourless, clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.67 (2H, s, H_4), 4.15 (2H, s, H_3), 3.37 (3H, s, H_5), 2.15 (3H, s, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 205.7 (C_2), 96.4 (C_4), 72.4 (C_3), 55.7 (C_5), 26.4 (C_1); **IR** ν_{max}/cm^{-1} (neat): 2952,

2897, 2829, 1719 (C=O stretch), 1441, 1425, 1401, 1356, 1217, 1152, 1114, 1078, 1041 (C-O stretch); **HRMS** (ESI): calcd. for $C_5H_9O_3^+$: 117.0552, found 117.0557, Δ 4.3 ppm

The observed characterisation data were consistent with literature values.[191]

1-(tert-Butyldimethylsilyloxy)propan-2-one (**322**)



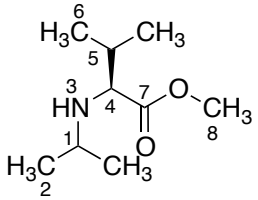
Hydroxyacetone (1.45 ml, 19 mmol), *tert*-butyldimethylsilyl chloride (3.65 g, 24 mmol) and imidazole (1.77 g, 26 mmol) were dissolved in DMF (20 ml) and stirred at rt for 16 h.

The reaction mixture was poured onto H_2O (100 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined organics were dried ($MgSO_4$), filtered and evapourated to provide the crude product. The crude product was purified by flash silica column chromatography eluting with 10% EtOAc in petroleum ether b.p. 40 – 60 °C to provide 1-[(*tert*-butyldimethylsilyl)oxy]propan-2-one as a colourless, clear oil (3.30 g, 18 mmol, 94%).

R_f (10% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.10 (2H, s, H_3), 2.11 (3H, s, H_1), 0.86 (9H, s, H_6), 0.04 (6H, s, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 209.0 (C_2), 69.4 (C_3), 25.8 (C_1), 25.6 (C_6), 18.2 (C_5), -5.6 (C_4); **^{29}Si NMR** (99 MHz, $CDCl_3$) δ: 22.1; **IR** ν_{max}/cm^{-1} (neat): 2956, 2929, 2893, 2857. 1719 (C=O stretch), 1475, 1467, 1356, 1253, 1116; **HRMS** (NSI): calcd. for $C_9H_{21}O_2Si^+$: 189.1305, found 189.1304, Δ 0.7 ppm

The observed characterisation data were consistent with literature values.[192]

(S)-Methyl 2-(isopropylamino)-3-methylbutanoate (**323**)



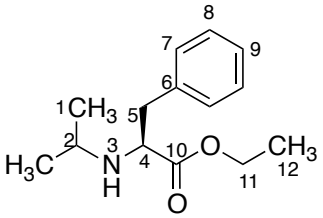
Crude material prepared by *General Procedure A* using L-valine methyl ester hydrochloride (7.38 g, 44 mmol) and acetone (3.8 ml, 51 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 85 °C, 5 mbar) to provide (*S*)-methyl 2-(isopropylamino)-3-methylbutanoate (5.17 g, 30 mmol, 68%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (3H, s, H_8), 3.07 (1H, d, *J* = 6.0, H_4), 2.60 (1H, septet, *J* = 6.2, H_2), 2.44 (1H, br s, H_3), 1.86 (1H, app. octet, *J* = 6.7, H_5), 1.04 (3H, d, *J* = 6.2, H_1), 0.98 (3H, d, *J* = 6.2, H_1),

0.93 (3H, d, *J* = 6.9, H_6), 0.91 (3H, d, *J* = 6.9, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.2 (C_7), 64.7 (C_4), 51.4 (C_8), 47.4 (C_2), 31.7 (C_5), 23.8 (C_1), 22.0 (C_1), 19.0 (C_6), 18.8 (C_6); **IR** ν_{max}/cm^{-1} (neat): 2963, 2876, 1734 (C=O stretch), 1466, 1435, 1382, 1369, 1337, 1301, 1263, 1239, 1199, 1163, 1123, 1058; **HRMS** (NSI): calcd. for $C_9H_{20}O_2N^+$: 174.1489, found 174.1485, Δ 2.0 ppm; **$[\alpha]_D^{31}$** = -6.4° (*c* = 1.0, $CHCl_3$)

The observed characterisation data were consistent with literature values.[193]

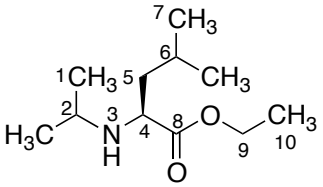
(S)-Ethyl 2-(isopropylamino)-3-phenylpropanoate (**324**)



Crude material prepared according to *General Prodecure A* using L-phenylalanine ethyl ester hydrochloride (11.49 g, 50 mmol) and acetone (7.3 ml, 99 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 130 °C, 0.8 mbar) to provide (*S*)-ethyl 2-(isopropylamino)-3-phenylpropanoate (9.88 g, 42 mmol, 84%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 – 7.23 (2H, m, H_7), 7.20 - 7.18 (1H, m, H_9), 7.17 – 7.15 (2H, m, H_8), 4.03 (2H, q, *J* = 7.2, H_{11}), 3.57 (1H, dd, *J* = 7.9, 6.6, H_4), 2.95 (1H, dd, *J* = 13.4, 6.6, H_5), 2.84 (1H, dd, *J* = 13.4, 7.9, H_5), 2.71 (1H, septet, *J* = 6.3, H_2), 1.69 (1H, br s, H_3), 1.08 (3H, t, *J* = 7.2, H_{12}), 1.01 (3H, d, *J* = 6.3, H_1), 0.96 (3H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.1 (C_{10}), 137.4 (C_6), 129.2 (C_8), 128.3 (C_7), 126.6 (C_9), 60.7 (C_4), 60.4 (C_{11}), 47.0 (C_2), 40.2 (C_5), 23.7 (C_1), 22.0 (C_1) 14.1 (C_{12}); **IR** ν_{max}/cm^{-1} (neat): 3676 (NH stretch), 2972, 2902, 1730 (C=O stretch), 1455, 1406, 1394, 1381, 1250, 142, 1229, 1174, 1076, 1066, 1057; **HRMS** (NSI): calcd. for $C_{14}H_{22}O_2N^+$: 236.1645, found 236.1644, Δ 0.4 ppm; **$[\alpha]_D^{31}$** = +20.2° (*c* = 1.0, $CHCl_3$)

(S)-Ethyl 2-(isopropylamino)-4-methylpentanoate (***325***)

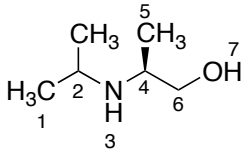


Crude material prepared according to *General Procedure A* using L-leucine ethyl ester hydrochloride (9.78 g, 50 mmol) and acetone (7.3 ml, 99 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 100 °C, 0.43 mbar) to provide (*S*)-ethyl 2-(isopropylamino)-4-methylpentanoate (8.29 g, 41 mmol, 82%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.16 (2H, qd, *J* = 7.2, 1.2, H_9), 3.34 (1H, t, *J* = 7.2, H_4), 2.83 (1H, br s, H_3), 2.70 (1H, septet, *J* = 6.3, H_2), 1.69 (1H, app. nonet, *J* = 6.9, H_6), 1.43 (2H, app. td, *J* = 7.2, 2.7, H_5), 1.26 (3H, t, *J* = 7.2, H_{10}), 1.04 (3H, d, *J* = 6.3, H_1), 1.00 (3H, d, *J* = 6.3, H_1), 0.92 (3H, d, *J* = 6.6, H_7), 0.89 (3H, d, *J* = 6.6, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.3 (C_8), 60.4 (C_9), 57.4 (C_4), 47.0 (C_2), 43.1 (C_5), 24.9 (C_6), 23.9 (C_1), 22.5 (C_7), 22.5 (C_7), 21.8 (C_1), 14.3 (C_{10}); **IR** ν_{max}/cm^{-1} (neat): 3676 (NH stretch), 2972,

2902, 1733 (C=O stretch), 1467, 1451, 1406, 1394, 1382, 1250, 1242, 1230, 1165, 1066; **HRMS** (NSI): calcd. for $C_{11}H_{24}O_2N^+$: 202.1802, found 202.1798, Δ 1.8 ppm; **$[\alpha]_D^{31}$** = -12.2° (*c* = 1.0, $CHCl_3$)

(S)-2-(Isopropylamino)propan-1-ol (***326***)

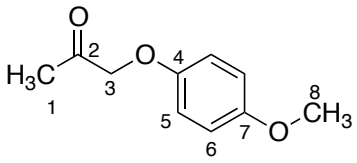


Crude material prepared according to *General Procedure C* using L-alaninol (3.76 g, 50 mmol) and acetone (10.0 ml, 136 mmol). The crude material was sufficently pure to be used without further purification providing (S)-2-(isopropylamino)propan-1-ol (5.86 g, 50 mmol. quant.) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.52 (1H, dd, *J* = 10.4, 4.1, H_6), 3.17 (1H, dd, *J* = 10.4, 7.4, H_6), 2.91 (1H, septet, *J* = 6.3, H_2), 2.82 (1H, app. sextet, *J* = 6.4, H_4), 1.06 (3H, d, *J* = 6.4, H_5), 1.01 (6H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 65.9 (C_6), 51.3 (C_4), 45.6 (C_2), 24.1 (C_5), 23.0 (C_1), 17.7 (C_1); **IR** ν_{max}/cm^{-1} (neat): 3288 (O-H stretch, H bonding), 2966, 1467, 1384, 1168, 1082, 1035; **HRMS** (APCI): calcd. for $C_6H_{16}NO^+$: 118.1232, found 118.1229, Δ 2.5 ppm; **$[\alpha]_D^{25}$** = +49.6° (*c* = 1.0, $CHCl_3$)

The observed characterisation data were consistent with literature values.[194]

1-(4-Methoxyphenoxy)propan-2-one (***327***)



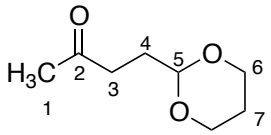
Chloroacetone (6.3 ml, 75 mmol) was added dropwise to a stirred suspension of 4-methoxyphenol (6.21 g, 50 mmol) and K_2CO_3 (10.0 g, 75 mmol) in acetone (100 ml). The reaction mixture was stirred at rt for 24 h.

The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product. The crude product was purified by flash silica column chromatography eluting with 20% EtOAc in petroleum ether b.p. 40 – 60 °C to provide 1-(4-methoxyphenoxy)propan-2-one (9.00 g, 50 mmol, quant.)

R_f (20% EtOAc in petroleum ether bp 40 – 60 °C): 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.82 (2H, s, H_5), 6.76 (2H, s, H_6), 4.48 (2H, s, H_3), 3.75 (3H, s, H_8), 2.25 (3H, s, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 206.5 (C_2), 154.5 (C_7), 151.9 (C_4), 115.6 (C_5), 114.8 (C_6), 73.8 (C_3), 55.7 (C_8), 26.6 (C_1); **IR** ν_{max}/cm^{-1} (neat): 2972, 2902, 1721 (C=O stretch), 1506, 1437, 1358, 1229, 1180, 1067, 1034; **HRMS** (NSI): calcd. for $C_{10}H_{16}O_3N^+$: 198.1125, found 198.1124, Δ 0.4 ppm

The observed characterisation data were consistent with literature values.[195]

4-(1,3-Dioxan-2-yl)butan-2-one (**328**)



2-(2-Bromoethyl)-1,3-dioxane (12.8 g, 66 mmol) was added dropwise to a stirred suspension of magnesium turnings (4.40 g, 185 mmol) in dry THF (40 ml) under a nitrogen atmosphere at rt. The reaction mixture was stirred at rt for 1 h.

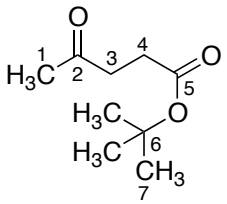
The resulting Grignard solution was added dropwise *via* canula to a stirred solution of acetyl chloride (6.4 ml, 90 mmol) in dry THF (80 ml) under a nitrogen atmosphere at rt. The reaction mixture was stirred for 15 h at rt.

The reaction mixture was then quenched by the addition of sat. aq. NH_4Cl (100 ml). The mixture was then concentrated under reduced pressure to remove THF. The residual aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product. The crude product was purified by flash silica column chromatography eluting with 20% EtOAc in petroleum ether b.p. 40 – 60 °C to provide 4-(1,3-dioxan-2-yl)butan-2-one (8.36 g, 53 mmol, 81%) as a pale yellow oil.

R_f (20% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.09; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.56 (1H, t, *J* = 4.9, H_5), 4.07 (2H, dd, *J* = 12.2, 4.8, H_6), 3.73 (2H, td, *J* = 12.2, 2.3, H_6), 2.55 (2H, t, *J* = 7.3, H_3), 2.13 (3H, s, H_1), 2.03 (1H, dqn, *J* = 13.4, 4.8, H_7), 1.86 (2H, td, *J* = 7.3, 4.9, H_4), 1.32 (1H, dqn, *J* = 13.4, 1.3, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 208.3 (C_2), 100.8 (C_5), 66.8 (C_6), 37.6 (C_3), 29.9 (C_1), 29.0 (C_4), 25.7 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2988, 2902, 1736 (C=O stretch), 1716, 1407, 1394, 1379, 1242, 1133, 1050; **HRMS** (NSI): calcd. for $C_8H_{15}O_3^+$: 159.1016, found 159.1012, Δ 2.3 ppm

The observed characterisation data were consistent with literature values.[196]

tert-Butyl 4-oxopentanoate (**329**)



N,N'-Dicyclohexylcarbodiimide (24.73 g, 120 mmol) was added to a stirred solution of levulinic acid (10.2 ml, 100 mmol), *tert*-butanol (20 ml, 209 mmol) and DMAP (3.67 g, 30 mmol) in CH_2Cl_2 (300 ml) at 0 °C. The reaction mixture was then stirred at rt for 24 h.

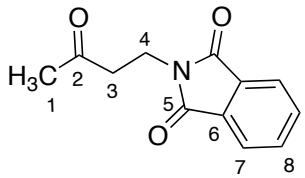
The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash silica column chromatrography eluting with 5% ethyl acetate in petroleum

ether b.p. 40 – 60 °C, followed by Kugelrohr distillation (b.p. ≈ 80 °C, 6 mbar) to provide *tert*-butyl 4-oxopentanoate (9.51 g, 55 mmol, 55%) as clear, colourless liquid.

R_f (5% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.07; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.68 (2H, t, *J* = 6.7, H_3), 2.48 (2H, t, *J* = 6.7, H_4), 2.17 (3H, s, H_1), 1.42 (9H, s, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 206.9 (C_2), 172.0 (C_5), 80.6 (C_6), 38.1 (C_3), 29.9 (C_1), 29.2 (C_4), 28.0 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2978, 2923, 1716 (C=O stretch, ketone), 1410, 1362, 1316, 1240, 1145, 1056, 1021; **HRMS** (NSI): calcd. for $C_9H_{17}O_3^+$: 173.1172, found 173.1171, Δ 0.7 ppm

The observed characterisation data were consistent with literature values.[197]

2-(3-Oxobutyl)isoindoline-1,3-dione (**330**)



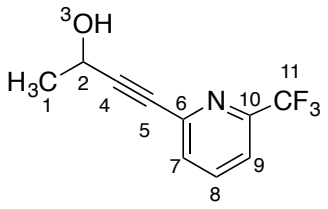
NaOEt (340 mg, 5 mmol) was added to a stirred solution of phthalimide (14.70 g, 100 mmol) and methyl vinyl ketone (8.1 ml, 100 mmol) in EtOH (20 ml). The reaction mixture was stirred at rt for 2 h and then at reflux for 2 h.

The reaction mixture was cooled to rt and diluted with H_2O (100 ml). The mixture was concentrated under reduced pressure to remove EtOH. The resulting aqueous phase was extracted with EtOAc (2 × 250 ml). The combined organics were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide 2-(3-oxobutyl)isoindoline-1,3-dione (17.94 g, 83 mmol, 83%) as an amorphous white powder, which was used without further purification.

m.p. 104 – 106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.83 (2H, dd, *J* = 5.5, 3.1, H_7), 7.71 (2H, dd, *J* = 5.5, 3.1, H_8), 3.95 (2H, t, *J* = 7.4, H_4), 2.87 (2H, t, *J* = 7.4, H_3), 2.18 (3H, s, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 205.8 (C_2), 168.1 (C_5), 134.3 (C_8), 132.0 (C_6), 123.3 (C_7), 41.6 (C_3), 33.0 (C_4), 29.9 (C_1); **IR** ν_{max}/cm^{-1} (neat): 1772 (C=O stretch, ketone), 1716 (C=O stretch, phthalimide), 1469, 1437, 1389, 1305, 1176, 1126, 1089, 1042; **HRMS** (NSI): calcd. for $C_{12}H_{12}O_3N^+$: 218.0812, found 218.0809, Δ 1.2 ppm

The observed characterisation data were consistent with literature values.[198]

4-(6-(Trifluoromethyl)pyridin-2-yl)but-3-yn-2-ol (**331**)



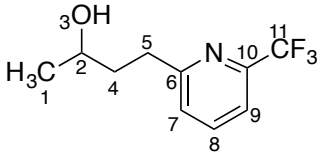
Bis(triphenylphosphine)palladium dichloride (492 mg, 0.40 mmol) was added to a stirred solution of 6-bromo-2-(trifluoromethyl)pyridine (7.91 g, 35 mmol), 3-butyn-2-ol (3.5 ml, 38 mmol) and copper iodide

(133.4 mg, 0.40 mmol) in Et_3N (100 ml) under an atmosphere of nitrogen at 0 °C. The reaction mixture was stirred for 1 h at 0 °C then 2 h at rt under nitrogen.

The reaction mixture was diluted with Et_2O (400 ml) and washed with H_2O (4 × 75 ml) and saturated brine (75 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with 50% Et_2O in petroleum ether b.p. 40 – 60 °C to provide 4-(6-(trifluoromethyl)pyridin-2-yl)but-3-yn-2-ol (7.53 g, 35 mmol, quant.) as a brown liquid.

R_f (50% Et_2O in petroleum ether b.p. 40 – 60 °C): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.82 (1H, app. t, *J* = 7.8, H_8), 7.58 (1H, d, *J* = 7.8, H_9), 7.57 (1H, d, *J* = 7.8, H_7), 4.78 (2H, app. q, *J* = 6.7, H_2), 3.23 (1H, br s, H_3), 1.55 (3H, d, *J* = 6.7, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 148.4 (q, $J_{C\text{-}F}$ = 34.8, C_{10}), 143.8 (C_6), 137.8 (C_8), 129.6 (C_7), 121.0 (q, $J_{C\text{-}F}$ = 275.0, C_{11}), 119.5 (C_9), 93.3 (C_4), 82.0 (C_5), 58.4 (C_2), 23.7 (C_1); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -68.1; **IR** ν_{max}/cm^{-1} (neat): 3350 (br, O-H stretch), 2986, 1590, 1459, 1421, 1340, 1274, 1243, 1188, 1138, 1105, 1083, 1042; **HRMS** (NSI): calcd. for $C_{10}H_9ONF_3$: 216.0631, found 216.0625, Δ 2.7 ppm

4-(6-(Trifluoromethyl)pyridin-2-yl)butan-2-ol (**332**)

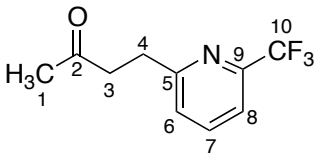


10% Pd/C (1.06 g, 1.0 mmol) was added to a stirred solution of 4-(6-(trifluoromethyl)pyridin-2-yl)but-3-yn-2-ol (6.99 g, 33 mmol) in CH_3OH (100 ml). The reaction vessel was evacuated and backfilled with hydrogen (× 3). The reaction mixture was then stirred at rt under an atmosphere of hydrogen for 16 h.

The reaction vessel was evacuated and backfilled with nitrogen (× 3). The reaction mixture was filtered through Celite®, eluting with CH_3OH (50 ml) and concentrated under reduced pressure to provide 4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-ol (6.97 g, 32 mmol, 98%) as a light brown liquid that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, app. t, *J* = 7.8, H_8), 7.51 (1H, d, *J* = 7.8, H_9), 7.37 (1H, d, *J* = 7.8, H_7), 3.88 – 3.82 (1H, m, H_2), 3.02 (2H, t, *J* = 7.4, H_5), 2.76 (1H, br s, H_3), 1.96 – 1.82 (2H, m, H_4), 1.23 (3H, d, *J* = 6.2, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.8 (C_6), 147.5 (q, $J_{C\text{-}F}$ = 34.6, C_{10}), 137.8 (C_8), 125.9 (C_7), 121.5 (q, $J_{C\text{-}F}$ = 274.3, C_{11}), 117.8 (C_9), 67.2 (C_2), 38.1 (C_4), 34.4 (C_5), 23.5 (C_1); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -68.1; **IR** ν_{max}/cm^{-1} (neat): 3361 (br OH stretch), 2970, 2929, 1602, 1464, 1436, 1342, 1183, 1117, 1092; **HRMS** (NSI): calcd. for $C_{10}H_{13}ONF_3$: 220.0944, found 220.0941, Δ 1.3 ppm

4-(6-(Trifluoromethyl)pyridin-2-yl)butan-2-one (**333**)



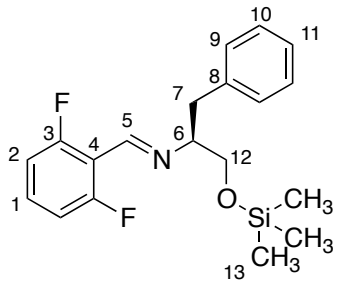
A solution of dry DMSO (4.7 ml, 66 mmol) in dry CH_2Cl_2 (40 ml) was added to a stirred solution of oxalyl chloride (2.9 ml, 34 mmol) in dry CH_2Cl_2 (40 ml) at -78 °C. The reaction mixture was stirred for 15 min at -78 °C.

A solution of 4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-ol (6.58 g, 30 mmol) in dry CH_2Cl_2 (40 ml) was then added dropwise to the reaction mixture at -78 °C. The reaction mixture was stirred for 1 h at -78 °C. The reaction was quenched with Et_3N (10.5 ml, 75 mmol) at -78 °C and the reaction mixture was subsequently allowed to warm to rt.

The reaction mixture was washed with H_2O (3 × 100 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with 30% EtOAc in petroleum ether b.p. 40 – 60 °C to provide 4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-one (5.72 g, 26 mmol, 88%) as a clear orange liquid.

R_f (30% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (1H, t, *J* = 7.8, H_7), 7.48 (1H, d, *J* = 7.8, H_6), 7.38 (1H, d, *J* = 7.8, H_8), 3.15 (2H, t, *J* = 6.9, H_4), 2.98 (2H, t, *J* = 6.9, H_3), 2.21 (3H, s, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 207.9 (C_2), 161.3 (C_5), 147.5 (q, $J_{C\text{-}F}$ = 34.4, C_9), 137.4 (C_7), 126.1 (C_8), 121.5 (q, $J_{C\text{-}F}$ = 274.0, C_{10}), 117.8 (C_6), 41.3 (C_3), 31.3 (C_4), 30.2 (C_1), **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -68.1; **IR** ν_{max}/cm^{-1} (neat): 2989, 2903, 1716 (C=O stretch), 1601, 1464, 1420, 1339, 1258, 1181, 1164, 1133, 1114, 1090; **HRMS** (NSI): calcd. for $C_{10}H_{11}ONF_3$: 218.0787, found 218.0786, Δ 0.6 ppm

(S,E)-N-(2,6-Difluorobenzylidene)-1-phenyl-3-((trimethylsilyl)oxy)propan-2-amine (**334**)



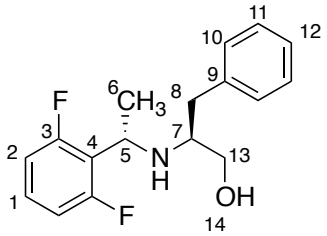
2,6-Difluorobenzaldehyde (6.5 ml, 60 mmol) was added to a stirred suspension of L-phenylalaninol (9.07 g, 60 mmol) and $MgSO_4$ (30 g, 250 mmol) in CH_2Cl_2 (80 ml). The reaction mixture was stirred at rt for 16 h.

The reaction mixture was filtered and washed through with CH_2Cl_2 (2 × 20 ml), Et_3N (9.3 ml, 67 mmol) was added to the filtrate, followed by dropwise addition of TMSCl (8.6 ml, 68 mmol). The reaction mixture was stirred for 3 h at rt.

The reaction mixture was filtered and washed through with CH_2Cl_2 (2 × 20 ml), the filtrate was then concentrated under reduced pressure. The residue was dissolved in 1:1 (v/v) Et_2O/Hexane (150 ml). The resulting precipitate was removed by filtration and the filtrate concentrated under reduced pressure to provide (*S*,*E*)-*N*-(2,6-difluorobenzylidene)-1-phenyl-3-((trimethylsilyl)oxy)propan-2-amine (19.22 g, 55 mmol, 92%) as an orange oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, s, H_5), 7.30 – 7.24 (3H, m, H_{10} & H_{11}), 7.22 – 7.20 (2H, m, H_9), 7.19 – 7.16 (1H, m, H_1), 6.89 (2H, app. t, *J* = 8.4, H_2), 3.85 (1H, dd, *J* = 10.2, 5.1, H_{12}), 3.77 (1H, dd, *J* = 10.2, 7.4, H_{12}), 3.54 – 3.48 (1H, m, H_6), 3.07 (1H, dd, *J* = 13.5, 4.5, H_7), 2.92 (1H, dd, *J* = 13.5, 8.7, H_7), 0.11 (9H, s, H_{13}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.6 (dd, $J_{C\text{-}F}$ = 256, 6.8, C_3), 152.1 (C_5), 138.8 (C_8), 131.2 (t, $J_{C\text{-}F}$ = 10.7, C_1), 129.7 (C_9), 128.2 (C_{10}), 126.1 (C_{11}), 113.9 (t, $J_{C\text{-}F}$ = 13.8, C_4), 111.9 (d, $J_{C\text{-}F}$ = 5.0, C_2), 111.7 (d, $J_{C\text{-}F}$ = 5.0, C_2), 76.3 (C_6), 65.6 (C_{12}), 38.9 (C_7), -0.4 (C_{13}); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -114.7, -113.3; **^{29}Si NMR** (100 MHz, $CDCl_3$) δ: 18.6; **IR** ν_{max}/cm^{-1} (neat): 3030, 2955, 2861, 1644 (C=N stretch), 1623, 1586, 1496, 1464, 1393, 1251, 1237, 1114, 1083, 1009

(S)-2-(((S)-1-(2,6-Difluorophenyl)ethyl)amino)-3-phenylpropan-1-ol (**335**)



A solution of (*S*,*E*)-*N*-(2,6-difluorobenzylidene)-1-phenyl-3-((trimethylsilyl)oxy)propan-2-amine (18.99 g, 55 mmol) in dry Et_2O (80 ml) was added dropwise over 30 min to a stirred solution of 1.6 M methyl lithium in THF (41 ml, 66 mmol) diluted with dry Et_2O (70 ml) under an atmosphere of nitrogen at -40 °C.

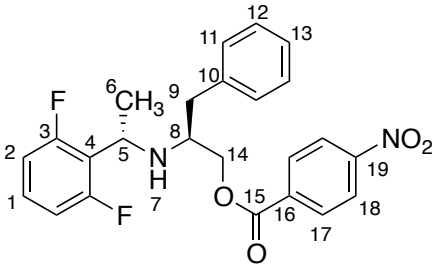
The reaction mixture was stirred at -40 °C for 3 h under nitrogen. The reaction mixture was quenched with 3 M aq. HCl (50 ml) at -40 °C, then allowed to warm to rt. The reaction mixture was diluted with H_2O (50 ml) and the phases were separated. The aqueous phase was re-extracted with Et_2O (2 × 30 ml). The aqueous layer was cooled to 0 °C and basified with solid NaOH until pH 12. The aqueous layer was then extracted with EtOAc (3 × 100 ml). The organic was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product as a single diastereomer.

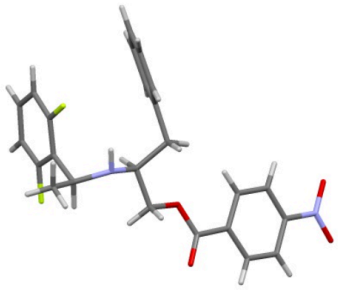
The crude product was purified by flash silica column chromatography eluting with 40% EtOAc in petroleum ether b.p. 40 – 60 °C to provide (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropan-1-ol (15.94 g, 55 mmol, quant.) as a yellow liquid.

R_f (40% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.20 – 7.15 (3H, m, H_{11} & H_{12}), 7.14 – 7.09 (1H, m, H_1), 6.97 – 6.94 (2H, m, H_{10}), 6.72 (2H, t, *J* = 8.5, H_2), 4.26 (1H, q, *J* = 7.0, H_5), 3.69 (1H, dd, *J* = 10.8, 3.5, H_{13}), 3.34 (1H, dd, *J* = 10.8, 2.4, H_{13}), 2.75 (1H, dd, *J* = 11.8, 4.9, H_8), 2.66 – 2.56 (2H, m, H_7 & H_8), 1.43 (3H, d, *J* = 7.0, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.5 (dd, $J_{C\text{-}F}$ = 247.0, 9.2, C_3), 138.2 (C_9), 129.0 (C_{10}), 128.4 (C_{11}), 128.3 (t, $J_{C\text{-}F}$ = 10.8, C_1), 126.3 (C_{12}), 119.6 (t, $J_{C\text{-}F}$ =

17.4, C_4), 111.6 (C_2), 111.4 (C_2), 61.4 (C_{13}), 57.6 (C_7), 45.7 (t, $J_{C\text{-}F}$ = 1.8, C_5), 38.6 (C_8), 21.4 (t, $J_{C\text{-}F}$ = 2.1, C_6); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -115.8; **IR** ν_{max}/cm^{-1} (neat): 3340 (O-H stretch), 3029, 2979, 2934, 2861, 1738, 1622, 1591, 1495, 1469, 1455, 1374, 1283, 1231, 1192, 1118, 1043, 1025; **HRMS** (NSI): calcd. for $C_{17}H_{20}ONF_2$: 292.1507, found 292.1502, Δ 1.9 ppm; $[\alpha]_D^{24}$ = -53.5° (*c* = 1.0, $CHCl_3$)

(S)-2-(((S)-1-(2,6-Difluorophenyl)ethyl)amino)-3-phenylpropyl 4-nitrobenzoate **(336)**





DMAP (6.1 mg, 0.05 mmol) was added to a stirred solution of (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropan-1-ol (291.3 mg, 1.0 mmol), 4-nitrobenzoyl chloride (222.7 mg, 1.2 mmol) and Et_3N (0.2 ml, 1.4 mmol) in CH_2Cl_2 (5 ml) at rt. The reaction mixture was stirred at rt for 16 h.

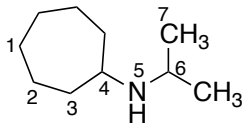
The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with sat. aq. $NaHCO_3$ (25 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with 20% EtOAc in petroleum ether b.p. 40 – 60 °C to provide (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropyl 4-nitrobenzoate (441 mg, 1.0 mmol, quant.) as a white powder.

m.p. 80 – 82 °C; **R_f** (20% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.30 (2H, dt, *J* = 9.0, 2.0, H_{18}), 8.20 (2H, d, *J* = 9.0, 2.0, H_{17}), 7.22 – 7.19 (3H, m, H_{12} & H_{13}), 7.15 – 7.10 (1H, m, H_1), 7.02 – 6.98 (2H, m, H_{11}), 6.72 (2H, t, *J* = 8.5, H_2), 4.45 (1H, dd, *J* = 11.1, 5.1, H_{14}), 4.39 (1H, q, *J* = 7.0, H_5), 4.33 (1H, dd, *J* = 11.2, 4.6, H_{14}), 2.99 – 2.94 (1H, m, H_8), 2.90 (1H, dd, *J* = 13.6, 5.5, H_9), 2.62 (1H, dd, *J* = 13.6, 8.5, H_9), 1.84 (1H, br s, H_7), 1.42 (3H, d, *J* = 7.0, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.6 (C_{15}), 161.3 (dd, $J_{C\text{-}F}$ = 246.6, 9.4, C_3), 150.6 (C_{19}), 137.5 (C_{10}), 135.6 (C_{16}), 130.8 (C_{17}), 128.9 (C_{11}), 128.6 (C_{12}), 128.3 (t, $J_{C\text{-}F}$ = 10.9, C_1), 126.6 (C_{13}), 123.6 (C_{18}), 119.7 (t, $J_{C\text{-}F}$ = 17.3, C_4), 111.6 (C_2), 111.4 (C_2), 67.7 (C_{14}), 55.8 (C_8), 46.6 (C_5), 39.2 (C_9), 21.4 (C_6); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -115.6; **IR** ν_{max}/cm^{-1} (neat): 2983, 2921, 2901, 1718 (C=O stretch), 1624, 1608, 1592, 1524, 1470, 1456, 1346, 1269, 1122, 1103, 1079, 1066, 1028, 1013; **HRMS** (NSI): calcd. for $C_{24}H_{23}O_4N_2F_2$: 441.1620, found 441.1611, Δ 2.1 ppm; $[\alpha]_D^{24}$ = -69.0° (*c* = 1.0, $CHCl_3$)

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the material.

4.6 Preparation of carbonylation substrates

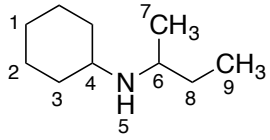
N-(Isopropyl)cycloheptylamine (**337**)



Crude material was prepared by *General Procedure C* using cycloheptylamine (6.4 ml, 50 mmol) and acetone (10.0 ml, 136 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 60 °C, 3 mbar) to provide *N*-(isopropyl)cycloheptylamine (5.22 g, 34 mmol, 67%) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.84 (1H, septet, *J* = 6.2, H_6), 2.66 (1H, qn, *J* = 4.2, H_4), 1.79 – 1.73 (2H, m, H_1), 1.62 – 1.24 (10H, m, H_1, H_2 & H_3), 0.99 (6H, d, *J* = 6.2, H_7), 0.69 (1H, br s, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 55.5 (C_4), 45.0 (C_6), 35.3 (C_1), 28.1 (C_3), 24.4 (C_2), 23.4 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2921, 2853, 1463, 1378, 1171, 1122, 1074; **HRMS** (NSI): calcd. for $C_{10}H_{22}N^+$: 156.1747, found 156.1746, Δ 0.5 ppm

N-(sec-Butyl)cyclohexanamine (**282**)

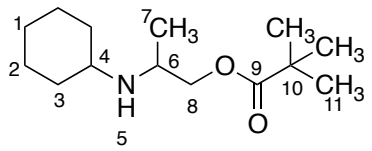


Crude material was prepared according to *General Procedure C* using cyclohexanone (5.2 ml, 50 mmol) and *sec*-butylamine (5.1 ml, 50 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 70 °C, 460 mbar) to provide *N*-(*sec*-butyl)cyclohexanamine (7.21 g, 46 mmol, 93%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.67 (1H, app. sextet, *J* = 6.3, H_6), 2.46 (1H, tt, *J* = 10.5, 3.9, H_4), 1.88 – 1.81 (2H, m, H_3), 1.72 – 1.67 (2H, m, H_2), 1.61 – 1.56 (1H, m, H_1), 1.47 – 1.38 (1H, m, H_8), 1.31 – 1.18 (3H, m, H_8 & H_2), 1.14 (1H, qnt, *J* = 12.2, 3.4, H_1), 1.05 – 0.93 (2H, m, H_3), 0.98 (3H, d, *J* = 6.3, H_7), 0.86 (3H, t, *J* = 7.5, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 53.5 (C_4), 50.7 (C_6), 34.5 (C_3), 34.0 (C_3), 30.0 (C_8), 26.2 (C_1), 25.3 (C_2), 25.2 (C_2), 20.5 (C_7), 10.3 (C_9); **IR** ν_{max}/cm^{-1} (neat): 2960, 2925, 2853, 1449, 1373, 1258, 1162, 1111; **HRMS** (NSI): calcd. for $C_{10}H_{22}N^+$: 156.1747, found 156.1742, Δ 3.0 ppm

The observed characterisation data were consistent with literature values.[199]

2-(Cyclohexylamino)propyl pivalate (**338**)

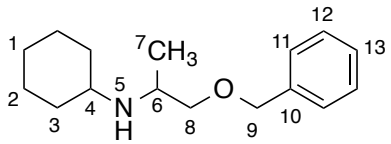


Crude material prepared according to *General Procedure G* using 2-(cyclohexylamino)propan-1-ol (3.15 g, 20 mmol).

The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 130 °C, 0.42 mbar) to provide 2-(cyclohexylamino)propyl pivalate (870 mg, 3.6 mmol, 18%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.97 (1H, dd, *J* = 10.9, 5.4, H_8), 3.93 (1H, dd, *J* = 10.9, 6.1, H_8), 3.07 (1H, app. sextet, *J* = 6.1, H_6), 2.52 (1H, tt, *J* = 10.5, 3.8, H_4), 1.90 – 1.83 (2H, m, H_3), 1.74 – 1.70 (2H m, H_2), 1.63 – 1.58 (1H, m, H_1), 1.31 – 1.20 (2H, m, H_2), 1.21 (9H, s, H_{11}), 1.16 (1H, tt, *J* = 12.3, 3.4, H_1), 1.07 (3H, d, *J* = 6.5, H_7), 1.07 – 0.98 (2H, m, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.3 (C_9), 68.3 (C_8), 53.7 (C_4), 48.4 (C_6), 38.8 (C_{10}), 34.2 (C_3), 33.9 (C_3), 27.2 (C_{11}), 26.1 (C_1), 25.2 (C_2), 25.1 (C_2), 18.4 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2973, 1729 (C=O stretch), 1480, 1451, 1406, 1394, 1382, 1250, 1230, 1146, 1057; **HRMS** (NSI): calcd. for $C_{14}H_{28}O_2N^+$: 242.2115, found 242.2113, Δ 0.6 ppm

N-(1-(Benzyloxy)propan-2-yl)cyclohexanamine (**339**)

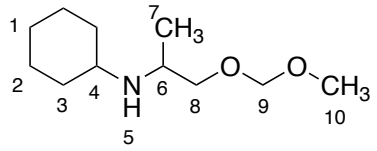


60% NaH (0.96 g, 24 mmol) was added portionwise to a stirred solution of 2-(cyclohexylamino)propan-1-ol (3.15 g, 20 mmol) in dry THF (30 ml) at rt under a nitrogen atmosphere. The reaction mixture was then stirred at reflux for 30 min. Benzyl chloride (2.3 ml, 20 mmol) was added dropwise to the reaction mixture. The reaction was then stirred at reflux for 16 h.

The reaction mixture was allowed to cool to rt and then quenched with H_2O (10 ml). The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (150 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with CH_2Cl_2 (100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 150 °C, 0.45 mbar) to provide *N*-(1-(benzyloxy)propan-2-yl)cyclohexanamine (1.44 g, 5.8 mmol, 29%) as a clear, colourless liquid

R_f (10% CH_3OH in CH_2Cl_2): 0.10; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.36 – 7.31 (4H, m, H_{11} & H_{12}), 7.30 – 7.27 (1H, m, H_{13}), 4.52 (2H, d, *J* = 1.6, H_9), 3.38 (1H, dd, *J* = 9.2, 4.8, H_8), 3.33 (1H, dd, *J* = 9.2, 6.7, H_8), 3.06 (1H, app. sextet, *J* = 6.3, H_6), 2.49 (1H, tt, *J* = 10.4, 3.8, H_4), 1.92 – 1.84 (2H, m, H_3), 1.74 – 1.70 (2H, m, H_2), 1.62 – 1.58 (1H, m, H_1), 1.30 – 1.21 (2H, m, H_2), 1.16 (1H, qnt, *J* = 12.1, 3.3, H_1), 1.10 – 0.95 (2H, m, H_3), 1.03 (3H, d, *J* = 6.3, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 138.5 (C_{10}), 128.3 (C_{12}), 127.6 (C_{11}), 127.5 (C_{13}), 75.1 (C_8), 73.1 (C_9), 53.5 (C_4), 49.0 (C_6), 34.8 (C_3), 33.6 (C_3), 26.2 (C_1), 25.4 (C_2), 25.2 (C_2), 18.2 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2988, 2902, 1451, 1407, 1382, 1250, 1230, 1067; **HRMS** (NSI): calcd. for $C_{16}H_{26}ON^+$: 248.2009, found 248.2007, Δ 0.8 ppm

N-(1-(Methoxymethoxy)propan-2-yl)cyclohexanamine (**340**)

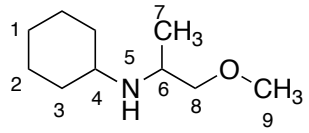


Crude material prepared according to *General Procedure B* using 1-(methoxymethoxy)propan-2-one (1.77 g, 15 mmol) and cyclohexylamine (1.7 ml, 15 mmol).

The crude product was purified by Kugelrohr distillation (b.p. ≈ 120 °C, 3 mbar) to provide *N*-(1-(methoxymethoxy)propan-2-yl)cyclohexanamine (521 mg, 2.6 mmol, 17%) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62 (2H, s, H_9), 3.45 (1H, dd, *J* = 9.5, 4.8, H_8), 3.36 (1H, dd, *J* = 9.5, 6.5, H_8), 3.35 (3H, s, H_{10}), 3.02 (1H, app. sextet, *J* = 6.4, H_6), 2.50 (1H, tt, *J* = 10.5, 3.7, H_4), 1.88 (2H, br t, *J* = 14.5, H_3), 1.71 (2H, br t, *J* = 13.1, H_2), 1.62 – 1.56 (2H, m, H_1 & H_2), 1.25 (2H, qnt, *J* = 12.5, 3.0, H_1 & H_2), 1.19 – 1.06 (2H, m, H_1 & H_2), 1.03 (3H, d, *J* = 6.4, H_7), 1.01 – 0.94 (2H, m, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 96.6 (C_9), 72.4 (C_8), 55.2 (C_{10}), 53.5 (C_4), 49.0 (C_6), 34.7 (C_3), 33.6 (C_3), 26.2 (C_2), 25.4 (C_2), 25.2 (C_1), 18.1 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2925, 2849, 1451, 1372, 1217, 1148, 1106, 1043 (C-O stretch); **HRMS** (NSI): calcd. for $C_{11}H_{24}O_2N^+$: 202.1802, found 202.1801, Δ 0.3 ppm

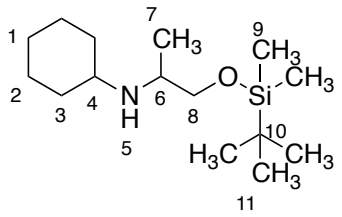
N-(1-Methoxypropan-2-yl)cyclohexanamine (**341**)



Crude material was prepared according to *General Procedure C* using 95% methoxyacetone (1.9 ml 20 mmol) and cyclohexylamine (2.3 ml). The crude product was purified by Kugelrohr distillation (b.p. ≈ 65 °C, 0.3 mbar) to provide *N*-(1-methoxypropan-2-yl)cyclohexanamine (2.62 g, 15 mmol, 77%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, d^6-DMSO) δ: 3.22 (3H, s, H_9), 3.16 (1H, dd, *J* = 9.1, 6.1, H_8), 3.10 (1H, dd, *J* = 9.1, 6.1, H_8), 2.89 (1H, app. sextet, *J* = 6.1, H_6), 2.44 (1H, tt, *J* = 10.2, 3.7, H_4), 1.77 (2H, br t, *J* = 15.4, H_3), 1.64 (2H, br dt, *J* = 12.7, 4.0, H_2), 1.53 (1H, br dt, *J* = 12.4, 4.0, H_1), 1.42 – 1.26 (1H, br s, H_5), 1.26 – 1.04 (3H, m, H_1 & H_2), 1.02 – 0.84 (2H, m, H_3), 0.90 (3H, d, J = 6.3, H_7); **^{13}C NMR** (100 MHz, d^6-DMSO) δ: 77.2 (C_8), 58.1 (C_9), 52.7 (H_4), 48.1 (C_6), 34.1 (C_3), 33.2 (C_3), 25.8 (C_1), 24.7 (C_2), 24.5 (C_2), 18.2 (C_7)**;** **IR** ν_{max}/cm^{-1} (neat): 2920, 2848, 1450, 1373, 1339, 1254, 1120, 1104 (C-O stretch); **HRMS** (NSI): calcd. for $C_{10}H_{22}ON^+$: 172.1696, found 172.1692, Δ 2.3 ppm

N-(1-((tert-Butyldimethylsilyl)oxy)propan-2-yl)cyclohexanamine (**342**)

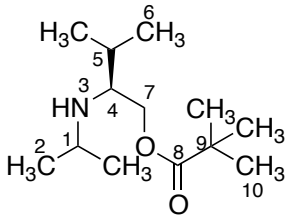


Crude material prepared according to *General Procedure B* using 1-(*tert*-butyldimethylsilyloxy)propan-2-one (2.83 g, 15 mmol) and cyclohexylamine (1.7 ml, 15 mmol)

The crude product was purified by Kugelrohr distillation (b.p. ≈ 80 °C, 0.3 mbar) to provide *N*-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)cyclohexanamine (2.38 g, 8.8 mmol, 58%) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47 (1H, dd, *J* = 9.8, 5.0, H_8), 3.38 (1H, dd, *J* = 9.8, 6.5, H_8), 2.86 (1H, app. sextet, *J* = 6.5, H_6), 2.47 (1H, tt, *J* = 10.4, 3.9, H_4), 1.87 – 1.81 (2H, m, H_3), 1.72 – 1.67 (2H, m, H_2), 1.60 – 1.55 (1H, m, H_1), 1.24 (2H, qnt, *J* = 12.4, 3.0, H_2), 1.13 – 0.99 (3H, m, H_1 & H_3), 0.96 (3H, d, *J* = 6.5, H_7), 0.87 (9H, s, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.4 (C_8), 53.5 (C_4), 51.0 (C_6), 34.8 (C_3), 33.6 (C_3), 26.2 (C_1), 25.9 (C_{11}), 25.3 (C_2), 25.1 (C_2), 18.2 (C_7), 17.8 (C_7), -5.38 (C_9); ^{29}Si NMR (99 MHz, $CDCl_3$) δ: 19.2; **IR** ν_{max}/cm^{-1} (neat): 2929, 2853, 1473, 1463, 1447, 1362, 1257, 1088, 1025; **HRMS** (NSI): calcd. for $C_{15}H_{34}ONSi^+$: 272.2404, found 272.2399, Δ 1.9 ppm

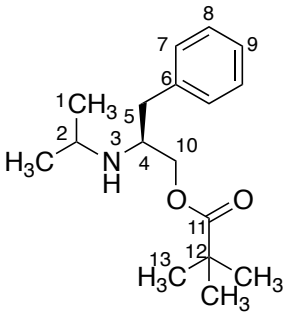
(S)-2-(Isopropylamino)-3-methylbutyl pivalate (**343**)



Crude material was prepared by *General Procedure D* using (*S*)-methyl 2-(isopropylamino)-3-methylbutanoate (3.47 g, 20 mmol). The crude material was then purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 115 °C, 1.5 mbar) to provide (*S*)-2-(isopropylamino)-3-methylbutyl pivalate (2.17 g, 9.4 mmol, 47%) as a clear, colourless oil.

R_f (10% CH_3OH in CH_2Cl_2): 0.41; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.09 (1H, dd, *J* = 11.3, 5.7, H_7), 3.97 (1H, dd, *J* = 11.3, 5.7, H_7), 2.87 (1H, septet, *J* = 6.3, H_2), 2.59 (1H, app. q, *J* = 5.3, H_4), 2.42 (1H, br s, H_3), 1.82 – 1.73 (1H, m, H_5), 1.19 (9H, s, H_{10}), 1.04 (3H, d, *J* = 6.3, H_1), 1.02 (3H, d, *J* = 6.3, H_1), 0.92 (6H, t, *J* = 6.8, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$): 178.5 (C_8), 64.9 (C_7), 58.7 (C_4), 46.7 (C_2), 38.8 (C_9), 30.0 (C_5), 27.2 (C_{10}), 23.7 (C_1). 23.1 (C_1), 18.7 (C_6), 18.6 (C_6); **IR** ν_{max}/cm^{-1} (neat): 3676 (NH stretch), 2972, 2902, 1729 (C=O stretch), 1480, 1454, 1406, 1394, 1382, 1281, 1250, 1242, 1230, 1149, 1057; **HRMS** (NSI): calcd. for $C_{13}H_{28}O_2N^+$: 230.2115, found 230.2109, Δ 2.4 ppm, **$[\alpha]_D^{31}$** = -6.1° (*c* = 1.0, $CHCl_3$)

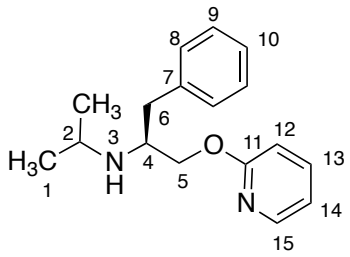
*(S)-2-(Isopropylamino)-3-phenylpropyl pivalate (**263**)*



Crude material was prepared by *General Procedure D* using (*S*)-ethyl 2-(isopropylamino)-3-phenylpropanoate (3.53 g, 15 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 160 °C, 0.68 mbar) to provide (*S*)-2-(isopropylamino)-3-phenylpropyl pivalate (3.07 g, 11 mmol, 55%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.31 – 7.27 (2H, m, H_8), 7.23 – 7.20 (1H, m, H_9), 7.18 - 7.16 (2H, m, H_7), 3.96 (2H, d, *J* = 5.3, H_{10}), 3.09 (1H, app. qn, *J* = 6.1, H_4), 2.88 (1H, septet, *J* = 6.3, H_2), 2.80 – 2.70 (2H, m, H_5), 1.23 (9H, s, H_{13}), 1.03 (3H, d, *J* = 6.3, H_1), 0.95 (3H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.3 (C_{11}), 138.3 (C_6), 129.2 (C_7), 128.5 (C_8), 126.4 (C_9), 65.6 (C_{10}), 55.0 (C_4), 46.0 (C_2), 38.8 (C_5), 27.2 (C_{13}), 23.5 (C_1), 22.9 (C_1); **IR** ν_{max}/cm^{-1} (neat): 3347 (N-H stretch), 2978, 2935; 1685 (C=O stretch), 1512, 1453, 1392, 1366, 1247, 1165 1099, 1044; **HRMS** (NSI): calcd. for $C_{17}H_{28}O_2N^+$: 278.2115, found 278.2114, Δ 0.2 ppm, **$[\alpha]_D^{31}$** = +3.3° (*c* = 1.0, $CHCl_3$)

(S)-N-Isopropyl-1-phenyl-3-(pyridin-2-yloxy)propan-2-amine (**344**)



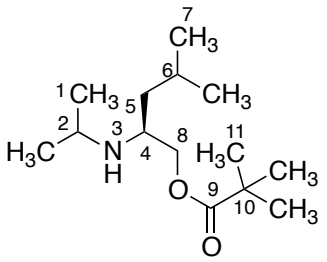
A 2.4 M solution of $LiAlH_4$ in THF (16.5 ml, 40 mmol) was added to a stirred solution of (*S*)-ethyl 2-(isopropylamino)-3-phenylpropanoate (4.03 g, 20 mmol) in THF (100 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h under nitrogen.

The reaction mixture was quenched with H_2O (5 ml) under nitrogen, 2 M aq. NaOH (5 ml) was then added, followed by H_2O (5 ml). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (75 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with EtOAc (50 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude amino alcohol, which was used without further purification.

The amino alcohol was then subjected to *General Procedure F* to provide the crude product. The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 165 °C, 0.5 mbar) to provide (*S*)-*N*-isopropyl-1-phenyl-3-(pyridin-2-yloxy)propan-2-amine (2.76 g, 10 mmol, 51%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.13 (1H, ddd, *J* = 5.0, 2.0, 0.8, H_{15}), 7.57 (1H, dddd, *J* = 15.5, 8.3, 7.1, 2.0, H_{13}), 7.29 – 7.26 (2H, m, H_9), 7.22 – 7.19 (3H, m, H_8 & H_{10}), 6.85 (1H, dddd, *J* = 12.1, 7.1, 5.0, 1.0, H_{14}), 6.77 (1H, dt, *J* = 8.3, 1.0, H_{12}), 4.20 (2H, br d, *J* = 5.0, H_5), 3.26 – 3.21 (1H, m, H_4), 2.95 (1H, septet, *J* = 6.3, H_2), 2.92 (1H, dd, *J* = 13.5, 7.1, H_6), 2.81 (1H, dd, *J* = 13.5, 6.6, H_6), 1.04 (3H, d, *J* = 6.3, H_1), 0.98 (3H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.9 (C_{11}), 146.9 (C_{15}), 139.0 (C_7), 138.5 (C_{13}), 129.4 (C_8), 128.4 (C_9), 126.2 (C_{10}), 116.7 (C_{14}), 111.0 (C_{12}), 67.2 (C_5), 55.6 (C_4), 46.0 (C_2), 38.8 (C_6), 23.6 (C_1), 23.1 (C_1); **IR** ν_{max}/cm^{-1} (neat): 2962, 1595, 1570, 1475, 1431, 1380, 1309, 1285, 1271, 1174, 1142, 1042, 1013; **HRMS** (NSI): calcd. for $C_{17}H_{23}ON_2^+$: 271.1805, found 271.1804, Δ 0.3 ppm ; **$[\alpha]_D^{24}$** = +23.5° (*c* = 1.0, $CHCl_3$)

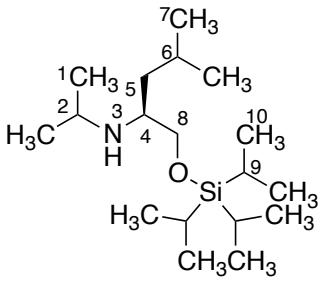
(S)-2-(Isopropylamino)-4-methylpentyl pivalate (**345**)



Crude material was prepared by *General Procedure D* using (*S*)-ethyl 2-(isopropylamino)-4-methylpentanoate (4.03 g, 20 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 110 °C, 0.8 mbar) to provide (*S*)-2-(isopropylamino)-4-methylpentyl pivalate (3.24 g, 13 mmol, 66%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.03 (1H, dd, *J* = 11.1, 5.0, H_8), 3.97 (1H, dd, *J* = 11.1, 5.0, H_8), 2.93 (1H, septet, *J* = 6.3, H_2), 2.86 (1H, app. ddd, *J* = 11.8, 7.1, 5.0, H_4), 2.55 (1H, br s, H_3), 1.69 (1H, septet, *J* = 6.6, H_6), 1.28 (2H, app. t, *J* = 7.1, H_5), 1.20 (9H, s, H_{11}), 1.05 (6H, d, *J* = 6.3, H_1), 0.92 (3H, d, *J* = 6.6, H_7), 0.89 (3H, d, *J* = 6.6, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.5 (C_9), 66.5 (C_8), 51.5 (C_4), 45.9 (C_2), 42.3 (C_5), 38.9 (C_{10}), 27.2 (C_{11}), 24.7 (C_6), 23.7 (C_1), 22.9 (C_7), 22.8 (C_7); **IR** ν_{max}/cm^{-1} (neat): 3669 (N-H stretch), 2959, 1730 (C=O stretch), 1480, 1465, 1396, 1381, 1367, 1282, 1229, 1148, 1057, 1036; **HRMS** (NSI): calcd. for $C_{14}H_{30}O_2N^+$: 244.2271, found 244.2267, Δ 1.7 ppm, **$[\alpha]_D^{31}$** = -5.4° (*c* = 1.0, $CHCl_3$)

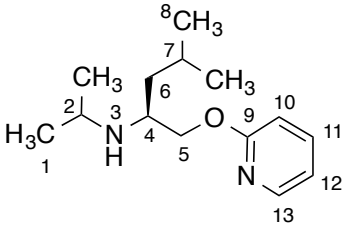
(S)-N-Isopropyl-4-methyl-1-((triisopropylsilyl)oxy)pentan-2-amine (***346***)



Crude material was prepared by *General Procedure E* using (*S*)-ethyl 2-(isopropylamino)-4-methylpentanoate (4.03 g, 20 mmol). The crude product was then purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (≈ 150 °C, 0.9 mbar) to provide (*S*)-*N*-isopropyl-4-methyl-1-((triisopropylsilyl)oxy)pentan-2-amine (3.42 g, 11 mmol, 54%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.67 (1H, dd, *J* = 9.8, 4.7, H_8), 3.50 (1H, dd, *J* = 9.7, 5.5, H_8), 2.89 (1H, septet, *J* = 6.3, H_2), 2.69 (1H, app. br qn, *J* = 5.8, H_4), 1.65 (1H, septet, *J* = 6.7, H_6), 1.32 – 1.21 (2H, m, H_5), 1.08 – 1.04 (27H, m, H_9 & H_{10}), 1.04 (6H, d, *J* = 6.3, H_1), 0.90 (3H, d, *J* = 6.7, H_7), 0.89 (3H, d, *J* = 6.7, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 65.3 (C_8), 54.4 (C_4), 45.6 (C_2), 42.1 (C_5), 25.0 (C_6), 23.6 (C_1), 23.2 (C_7), 22.9 (C_7), 18.0 (C_{10}). 11.9 (C_9); **^{29}Si NMR** (99 MHz, $CDCl_3$) δ: 12.5; **IR** ν_{max}/cm^{-1} (neat): 2957, 2867, 1464, 1380, 1367, 1335, 1249, 1172, 1099, 1069, 1013; **HRMS** (NSI): calcd. for $C_{18}H_{42}ONSi^+$: 316.3030, found 316.3023, Δ 2.3 ppm, **$[\alpha]_D^{31}$** = +1.5° (*c* = 1.0, $CHCl_3$)

(S)-N-Isopropyl-4-methyl-1-(pyridin-2-yloxy)pentan-2-amine (**347**)



A 2.4 M solution of $LiAlH_4$ in THF (16.5 ml, 40 mmol) was added to a stirred solution of (*S*)-ethyl 2-(isopropylamino)-4-methylpentanoate (4.89 g, 20 mmol) in THF (100 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h under nitrogen.

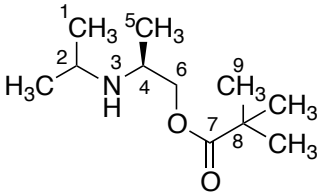
The reaction mixture was quenched with H_2O (5 ml) under nitrogen, 2 M aq. NaOH (5 ml) was then added, followed by H_2O (5 ml). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (75 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with EtOAc (50 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude amino alcohol, which was used without further purification.

The crude product was subjected to *General Procedure F* to provide the crude product. The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10%

CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 150 °C, 0.9 mbar) to provide (*S*)-*N*-isopropyl-4-methyl-1-(pyridin-2-yloxy)pentan-2-amine (1.08 g, 4.6 mmol, 23%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.14 (1H, ddd, *J* = 5.0, 2.0, 0.8, H_{13}), 7.56 (1H, dddd, *J* = 12.1, 8.3, 7.1, 2.0, H_{11}), 6.85 (1H, dddd, *J* = 12.1, 7.1, 5.0, 0.8, H_{12}), 6.75 (dt, *J* = 8.3, 0.8, H_{10}), 4.28 (1H, dd, *J* = 10.6, 4.4, H_5), 4.17 (1H, dd, *J* = 10.6, 5.3, H_5), 3.01 (1H, qn, *J* = 7.6, H_4), 2.97 (1H, septet, *J* = 6.3, H_2), 1.75 (1H, app. nonet, *J* = 6.8, H_7), 1.45 – 1.39 (1H, m, H_6), 1.37 – 1.32 (1H, m, H_6), 1.06 (3H, d, *J* = 6.3, H_1), 1.05 (3H, d, *J* = 6.3, H_1), 0.94 (3H, d, *J* = 6.6, H_8), 0.91 (3H, d, *J* = 6.6, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.0 (C_9), 146.9 (C_{13}), 138.5 (C_{11}), 116.6 (C_{12}), 111.1 (C_{10}), 68.2 (C_5), 51.8 (C_4), 45.8 (C_2), 42.4 (C_6), 24.8 (C_7), 23.8 (C_1), 23.4 (C_1), 23.0 (C_8), 22.9 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2972, 1595, 1571, 1475, 1453, 1431, 1407, 1394, 1382, 1311, 1285, 1250, 1066; **HRMS** (NSI): calcd. for $C_{14}H_{25}ON_2^+$: 237.1961, found 237.1961, Δ 0.2 ppm, **$[\alpha]_D^{24}$** = -1.7° (*c* = 1.0, $CHCl_3$)

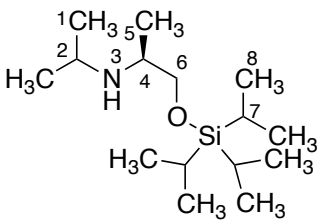
(S)-2-(Isopropylamino)propyl pivalate (**348**)



Crude material prepared according to *General Procedure G* using (S)-2-(isopropylamino)propan-1-ol (2.93 g, 25 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 130 °C, 1.3 mbar) to provide (*S*)-2-(isopropylamino)propyl pivalate (3.78 g, 19 mmol, 75%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.95 (1H, d, *J* = 10.9, 5.3, H_6), 3.91 (1H, d, *J* = 10.9, 5.8, H_6), 2.99 (1H, app. sextet, *J* = 5.8, H_4), 2.90 (1H, septet, *J* = 6.2, H_2), 1.74 (1H, br s, H_3), 1.18 (9H, s, H_9), 1.04 (3H, d, *J* = 6.6, H_5), 1.03 (3H, d, *J* = 6.2, H_1), 1.01 (3H, d, *J* = 6.2, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.3 (C_7), 68.1 (C_6), 48.8 (C_4), 45.6 (C_2), 38.8 (C_8), 27.2 (C_9), 23.5 (C_1), 23.2 (C_1), 18.3 (C_5); **IR** ν_{max}/cm^{-1} (neat): 3676 (NH stretch), 2972, 2902, 1729 (C=O stretch), 1480, 1453, 1406, 1394, 1381, 1282, 1250, 1242, 1230, 1146, 1066; **HRMS** (NSI): calcd. for $C_{11}H_{24}O_2N^+$: 202.1802, found 202.1799, Δ 1.3 ppm, **$[\alpha]_D^{31}$** = +8.4° (*c* = 1.0, $CHCl_3$)

(S)-N-Isopropyl-1-((triisopropylsilyl)oxy)propan-2-amine (**349**)

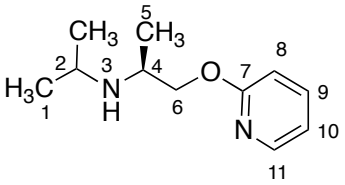


Triisopropylsilyl chloride (7.0 ml, 33 mmol) was added to a stirred solution of (S)-2-(isopropylamino)propan-1-ol (2.93 g, 25 mmol) and imidazole (2.23 g, 33 mmol) in DMF (20 ml). The reaction mixture was stirred at rt for 16 h.

The reaction mixture was diluted with EtOAc (150 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The aqueous layer was further extracted with EtOAc (100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. The combined fractions were then concentrated under reduced pressure and then purified by Kugelrohr distillation (≈ 140 °C, 1.3 mbar) to provide (*S*)-*N*-isopropyl-1-((triisopropylsilyl)oxy)propan-2-amine (4.89 g, 18 mmol, 72%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.60 (1H, dd, *J* = 9.6, 4.9, H_6), 3.49 (1H, dd, *J* = 9.6, 6.5, H_6), 2.89 (1H, septet, *J* = 6.3, H_2), 2.84 (1H, app. sextet, *J* = 6.2, H_4), 1.31 (1H, br s, H_3), 1.10 – 1.03 (21H, m, H_7 & H_8), 1.03 (6H, d, *J* = 6.3, H_1), 1.00 (3H, d, *J* = 6.2, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.5 (C_6), 51.8 (C_4), 45.5 (C_2), 24.1 (C_1), 23.0 (C_1), 18.0 (C_8), 17.9 (C_5), 11.9 (C_7); **^{29}Si** NMR (99 MHz, $CDCl_3$): 12.6; **IR** ν_{max}/cm^{-1} (neat): 3676, 2972, 2902, 1453, 1406, 1394, 1382, 1250, 1242, 1230, 1066; **HRMS** (NSI): calcd. for $C_{15}H_{36}ONSi^+$: 274.2561, found 274.2554, Δ 2.4 ppm, **$[\alpha]_D^{31}$** = +7.9° (*c* = 1.0, $CHCl_3$)

(S)-N-Isopropyl-1-(pyridin-2-yloxy)propan-2-amine (**350**)

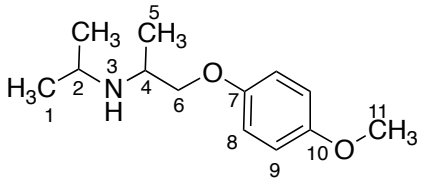


Crude material prepared according to *General Procedure F* using (S)-2-(isopropylamino)propan-1-ol (2.93 g, 25 mmol).

The crude product was purified by flash silica column chromatography eluting with 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 110 °C, 0.9 mbar) to provide (*S*)-*N*-isopropyl-1-(pyridin-2-yloxy)propan-2-amine (1.48 g, 7.6 mmol, 30%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.13 (1H, ddd, *J* = 5.0, 2.0, 0.8, H_{11}), 7.55 (1H, dddd, *J* = 15.4, 9.2, 7.2, 2.0, H_9), 6.85 (1H, dddd, *J* = 12.2, 7.1, 5.1, 0.9, C_{10}), 6.74 (1H, dt, *J* = 8.4, 0.9, C_8), 4.22 (1H, dd, *J* = 10.4, 4.9, H_6), 4.15 (1H, dd, *J* = 10.4, 6.1, H_6), 3.17 (1H, app. sextet, *J* = 6.4, H_4), 2.98 (1H, septet, *J* = 6.3, H_2), 1.15 (3H, d, *J* = 6.4, H_5), 1.08 (3H, d, *J* = 6.3, H_1), 1.05 (3H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.9 (C_7), 146.9 (C_{11}), 138.5 (C_9), 116.7 (C_{10}), 111.0 (C_8), 69.9 (C_6), 49.1 (C_4), 45.5 (C_2), 23.7 (C_1), 23.1 (C_1), 18.3 (C_5); **IR** ν_{max}/cm^{-1} (neat):2961, 2871, 1594, 1571, 1475, 1466, 1431, 1379, 1310, 1284, 1171, 1142, 1043, 1019; **HRMS** (NSI): calcd. for $C_{11}H_{19}ON_2^+$: 195.1492, found 195.1489, Δ 1.5 ppm, **$[\alpha]_D^{24}$** = +7.0° (*c* = 1.0, $CHCl_3$)

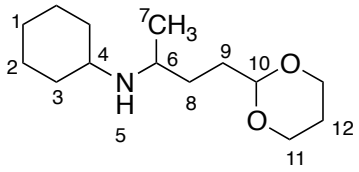
N-Isopropyl-1-(4-methoxyphenoxy)propan-2-amine (**351**)



Crude material was prepared using *General Procedure A* using 1-(4-methoxyphenoxy)propan-2-one (4.51 g, 25 mmol) and isopropylamine (2.2 ml, 25 mmol). The crude product was then purified by Kugelrohr distillation (b.p. ≈ 150 °C, 0.51 mbar) to provide *N*-isopropyl-1-(4-methoxyphenoxy)propan-2-amine (2.23 g, 10 mmol, 40%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.85 – 6.80 (4H, m, H_8 & H_9), 3.81 (2H, d, *J* = 5.5, H_6), 3.76 (3H, s, H_{11}), 3.16 (1H, app. sextet, *J* = 6.3, H_4), 2.98 (1H, septet, *J* = 6.3, H_2), 1.16 (3H, d, *J* = 6.3, H_5), 1.11 (3H, d, *J* = 6.3, H_1), 1.07 (3H, d, *J* = 6.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.9 (C_{10}), 153.2 (C_7), 115.6 (C_8 or C_9), 114.6 (C_8 or C_9), 73.4 (C_6), 55.7 (C_{11}), 49.4 (C_4), 45.7 (C_2), 23.7 (C_1), 22.9 (C_1), 18.0 (C_5); **IR** ν_{max}/cm^{-1} (neat): 2970, 2902, 1652, 1507, 1464, 1380, 1228, 1178, 1043; **HRMS** (NSI): calcd. for $C_{13}H_{22}O_2N^+$: 224.1645, found 224.1643, Δ 0.9 ppm

N-(4-(1,3-Dioxan-2-yl)butan-2-yl)cyclohexanamine (**352**)



$MgSO_4$ (19.26 g, 160 mmol) was added to a stirred solution of 4-(1,3-dioxan-2-yl)butan-2-one (6.33 g, 40 mmol) and cyclohexylamine (4.6 ml, 40 mmol) in CH_2Cl_2 (200 ml). The reaction mixture was stirred at rt for 16 h under nitrogen.

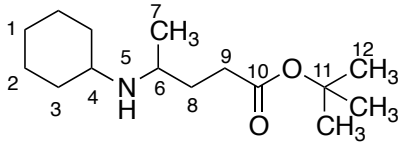
The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3OH (200 ml), $NaBH_4$ (1.71 g, 45 mmol) was added portionwise to the resulting solution at 0 °C. The reaction mixture was then stirred at rt for 16 h.

The reaction was quenched with H_2O (10 ml) and the reaction mixture was concentrated. The residue was diluted with EtOAc (200 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 140 °C, 0.4 mbar) to provide *N*-(4-(1,3-dioxan-2-yl)butan-2-yl)cyclohexanamine (898 mg, 3.7 mmol, 9%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.07; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.51 (1H, t, *J* = 5.0, H_{10}), 4.10 (2H, dd, *J* = 12.2, 5.0, H_{11}), 3.75 (2H, br t, *J* = 12.5, H_{11}), 2.75 (1H, app. sextet, *J* = 6.3, H_6), 2.48 (1H, tt, *J* = 10.3, 3.7, H_4), 2.07 (1H, qt, *J* = 12.5, 5.0, H_{12}), 1.86 – 1.81 (2H, m, H_3), 1.73 – 1.67 (2H, m, H_2), 1.63 – 1.57

(3H, m, H_1 & H_9), 1.53 – 1.46 (1H, m, H_8), 1.38 – 1.31 (2H, m, H_8 & H_{12}), 1.30 – 1.19 (2H, m, H_2), 1.15 (1H, tt, *J* = 12.1, 3.3, H_1), 1.05 – 0.94 (2H, m, H_3), 1.00 (3H, d, *J* = 6.3, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 102.5 (C_{10}), 66.9 (C_{11}), 53.5 (C_4), 49.1 (C_6), 34.5 (C_3), 34.0 (C_3), 31.9 (C_9), 31.7 (C_8), 26.2 (C_1), 25.8 (C_{12}), 25.3 (C_2), 25.2 (C_2), 21.2 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2972, 2902, 1450, 1406. 1394, 1380, 1250, 1143, 1066; **HRMS** (NSI): calcd. for $C_{14}H_{28}O_2N^+$: 242.2115, found 242.2114, Δ 0.2 ppm

tert-Butyl 4-(cyclohexylamino)pentanoate (**353**)

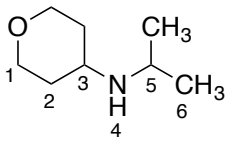


Crude material was prepared according to *General Procedure C* using *tert*-butyl 4-oxopentanoate (8.61 g, 50 mmol), cyclohexylamine (5.7 ml, 50 mmol).

The crude product was purified by Kugelrohr distillation (b.p. ≈ 110 °C, 0.9 mbar) to provide *tert*-butyl 4-(cyclohexylamino)pentanoate (6.10 g, 24 mmol, 48%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.76 (1H, app. sextet, *J* = 6.4, H_6), 2.49 (1H, tt, *J* = 10.5, 3.7, H_4), 2.25 (2H, td, *J* = 7.8, 3.6, H_9), 1.87 – 1.82 (2H, m, H_3), 1.77 – 1.64 (3H, m, H_2 & H_8), 1.61 – 1.51 (3H, m, H_1 & H_8), 1.43 (9H, s, H_{12}), 1.28 – 0.94 (5H, m, H_1, H_2 & H_3), 1.02 (3H, d, *J* = 6.4, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.3 (C_{10}), 80.0 (C_{11}), 53.5 (C_4), 48.8 (C_6), 33.9 (C_3), 32.6 (C_8), 32.4 (C_9), 28.2 (C_{12}), 26.2 (C_1), 25.3 (C_2), 25.1 (C_2), 20.9 (C_7); **IR** ν_{max}/cm^{-1} (neat): 3663 (NH stretch), 2978, 2923, 1727 (C=O stretch, ester), 1448, 1408, 1391, 1367, 1253, 1147, 1064; **HRMS** (NSI): calcd. for $C_{15}H_{30}O_2N^+$: 256.2271, found 256.2271, Δ 0.0 ppm

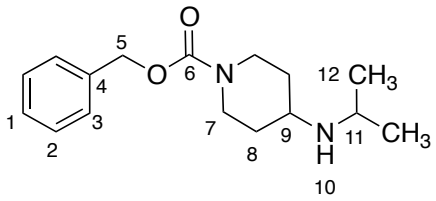
N-Isopropyltetrahydro-2H-pyran-4-amine (**354)**



Crude material prepared according to *General Procedure C* using dihydro-2*H*-pyran-4(3*H*)-one (5.0 g, 50 mmol) and isopropylamine (4.3 ml, 50 mmol). The crude product was purified by Kugelrohr distillation (b.p. ≈ 170 °C, 1 atm) to provide *N*-isopropyltetrahydro-2*H*-pyran-4-amine (5.40 g, 38 mmol, 75%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (2H, ddd, *J* = 12.0, 4.3, 2.5, H_1), 3.37 (2H, td, *J* = 12.0, 2.2, H_1), 2.97 (1H, septet, *J* = 6.2, H_5), 2.72 (1H, tt, *J* = 10.7, 4.1, H_3), 1.79 (2H, ddd, *J* = 12.9, 4.1, 2.2, H_2), 1.31 (2H, app. qd, *J* = 11.5, 4.1, H_2), 1.02 (6H, d, *J* = 6.2, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.1 (C_1), 50.7 (C_3), 44.2 (C_5), 34.4 (C_2), 23.3 (C_6); **IR** ν_{max}/cm^{-1} (neat): 2961, 2839, 1467, 1443, 1379, 1360, 1337, 1236, 1172, 1142, 1112, 1084, 1016, 1004; **HRMS** (NSI): calcd. for $C_8H_{18}ON^+$: 144.1383, found 144.1380, Δ 2.0 ppm

Benzyl 4-(isopropylamino)piperidine-1-carboxylate (**355**)



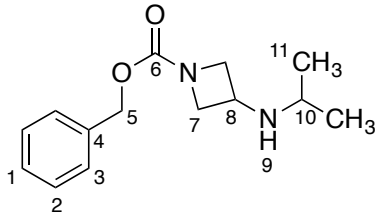
4 Å molecular sieves (500 mg) were added to a stirred solution of 1-CBz-4-piperidone (4.67 g, 20 mmol) in isopropylamine (20.0 ml, 233 mmol). The reaction mixture was stirred for 16 h at rt.

The reaction mixture was filtered through Celite® and eluted with EtOAc (50 ml). The filtrate was concentrated under reduced pressure and the residue was dissolved in CH_3OH (60 ml). $NaBH_4$ (2.27 g, 60 mmol) was added to the solution at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 16 h.

The reaction mixture was quenched with H_2O (10 ml) and concentrated under reduced pressure. The residue was dissolved in EtOAc (100 ml) and washed with sat. aq. $NaHCO_3$ (2 × 50 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation (b.p. ≈ 160 °C, 0.8 mbar) to provide benzyl 4-(isopropylamino)piperidine-1-carboxylate (5.12 g, 20 mmol, 99%) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.28 (5H, m, H_1, H_2 & H_3), 5.12 (2H, s, H_5), 4.13 (2H, br s, H_7), 2.97 (1H, septet, J = 6.2, H_{11}) 2.86 (2H, br t, J = 10.9, H_7), 2.70 (1H, tt, J = 10.4, 3.9, H_9), 1.86 (2H, br d, J = 8.2, H_8), 1.21 (2H, br qd, J = 12.4, 3.9, H_8), 1.04 (6H, d, J = 6.2, H_{12}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.3 (C_6), 136.9 (C_4), 128.5 (C_1, C_2 or C_3), 127.9 (C_1, C_2 or C_3), 127.8 (C_1, C_2 or C_3), 67.0 (C_5), 51.6 (C_9), 44.6 (C_{11}), 43.1 (C_7), 33.2 (br C_8), 23.4 (C_{12}); **IR** ν_{max}/cm^{-1} (neat): 2964, 2861, 1693 (C=O stretch, carboxybenzyl), 1429, 1362, 1270, 1225, 1165, 1134, 1112, 1088, 1068, 1013; **HRMS** (NSI): calcd. for $C_{16}H_{25}O_2N_2^+$: 277.1911, found 277.1916, Δ 2.0 ppm

Benzyl 3-(isopropylamino)azetidine-1-carboxylate (**356**)

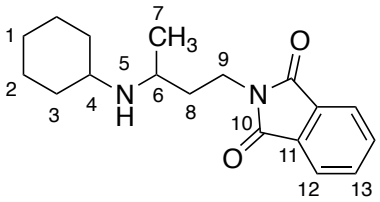


Crude material was prepared according to *General Procedure A* using benzyl 3-oxoazetidine-1-carboxylate (4.1 g, 20 mmol) and isopropylamine (2.0 ml, 23 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then diluted with Et_2O (25 ml). The HCl salt of the amine was prepared by addition of 2 M HCl in Et_2O (12.5 ml, 25 mmol), which was recrystallised from CH_3OH. The HCl salt was then neutralised using sat. aq. $NaHCO_3$ (60 ml) and extracted using EtOAc (3 × 100 ml). The resulting amine was then purified by Kugelrohr distillation (b.p. ≈

130 °C, 0.5 mbar) to provide benzyl 3-(isopropylamino)azetidine-1-carboxylate (1.43 g, 5.7 mmol, 29%) as a clear, colourless liquid.

R_f (5% CH_3OH in CH_2Cl_2): 0.11; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 – 7.33 (4H, m, H_2 & H_3), 7.32 – 7.28 (1H, m, H_1), 5.08 (2H, s, H_5), 4.21 – 4.16 (2H, m, H_7), 3.70 – 3.66 (3H, m, H_7 & H_8), 2.81 (1H, septet, *J* = 6.3, H_{10}), 1.03 (6H, d, *J* = 6.3, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.4 (C_6), 136.7 (C_4), 128.5 (C_2), 128.0 (C_1 & C_3), 66.6 (C_5), 57.8 (br, C_7), 47.3 (C_{10}), 46.4 (C_8), 23.2 (C_{11}); **IR** ν_{max}/cm^{-1} (neat): 2962, 2877, 1700 (C=O stretch), 1449, 1415, 1350, 1288, 1120, 1050; **HRMS** (NSI): calcd. for $C_{14}H_{21}O_2N_2^+$: 249.1598, found 249.1591, Δ 2.6 ppm

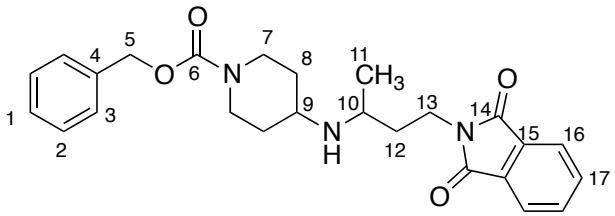
2-(3-(Cyclohexylamino)butyl)isoindoline-1,3-dione (**357**)



Crude material was prepared according to *General Procedure A* using cyclohexylamine (3.4 ml, 30 mmol) and 2-(3-oxobutyl)isoindoline-1,3-dione (6.52 g, 30 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of 1% Et_3N in CH_2Cl_2 to 1% Et_3N, 5% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 165 °C, 0.3 mbar) to provide 2-(3-(cyclohexylamino)butyl)isoindoline-1,3-dione as a viscous yellow oil (1.13 g, 3.8 mmol, 13%).

R_f (5% CH_3OH in CH_2Cl_2): 0.19; **^{1}H NMR** (400 MHz, d^6-DMSO) δ: 7.86 – 7.81 (4H, m, H_{12} & H_{13}), 3.68 – 3.56 (2H. m, H_9), 2.73 (1H, app. sextet, *J* = 6.1, H_6), 2.41 (1H, tt, *J* = 10.2, 3.7, H_4), 1.74 – 1.67 (2H, m, H_3), 1.64 – 1.54 (4H, m, H_2 & H_8), 1.52 – 1.49 (1H, m, H_1), 1.20 – 1.01 (3H, m, H_1 & H_2), 0.99 (3H, t, *J* = 6.1, H_7), 0.95 – 0.84 (2H, m, H_3); **^{13}C NMR** (100 MHz, d^6-DMSO) δ: 167.9 (C_{10}), 134.3 (C_{12}), 131.7 (C_{11}), 122.9 (C_{13}), 52.5 (C_4), 46.7 (C_6), 35.4 (C_8), 35.0 (C_9), 33.8 (C_3), 33.0 (C_3), 25.9 (C_1), 24.6 (C_2), 24.4 (C_2), 20.7 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2924, 2853, 1772 (C=O stretch), 1705 (C=O stretch), 1613, 1467, 1447, 1395, 1364, 1157, 1054; **HRMS** (NSI): calcd. for $C_{18}H_{25}O_2N_2^+$: 301.1911, found 301.1910, Δ 0.2 ppm

Benzyl 4-((4-(1,3-dioxoisoindolin-2-yl)butan-2-yl)amino)piperidine-1-carboxylate (**358**)

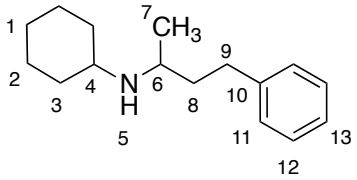


Crude material was prepared according to *General Procedure A* using benzyl 4-aminopiperidine-1-carboxylate hydrochloride (4.74 g 18 mmol) and 2-(3-oxobutyl)isoindoline-1,3-dione (3.80 g, 18 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then diluted with Et_2O (25 ml). The HCl salt of the amine was then prepared by addition of 2

M HCl in Et_2O (10 ml, 20 mmol), which was recrystallised from CH_3OH. The HCl salt was then neutralised using sat. aq. $NaHCO_3$ (60 ml) and the free amine extracted using EtOAc (3 × 100 ml). Removal of the solvent provided benzyl 4-((4-(1,3-dioxoisoindolin-2-yl)butan-2-yl)amino)piperidine-1-carboxylate (1.79 g, 4.1 mmol, 24%) as a viscous, pale yellow oil.

R_f (5% CH_3OH in CH_2Cl_2): 0.12; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (2H, dd, *J* = 5.5, 3.2, H_{17}), 7.73 (2H, dd, *J* = 5.5, 3.2, H_{16}), 7.40 – 7.33 (4H, m, H_2 & H_3), 7.32 – 7.28 (1H, m, H_1), 5.14 (2H, s, H_5), 4.10 (2H, br s, H_7), 3.84 – 3.73 (2H, m, H_{13}), 2.97 – 2.84 (3H, m, H_7 & H_{10}), 2.80 – 2.72 (1H, m, H_9), 1.88 – 1.79 (2H, m, H_8), 1.79 – 1.73 (2H, m, H_{12}), 1.32 – 1.19 (2H, m, H_8), 1.14 (3H, d, *J* = 6.3, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.5 (C_{14}), 155.2 (C_6), 136.9 (C_4), 133.9 (C_{16}), 132.2 (C_{15}), 128.5 (C_2 or C_3), 127.9 (C_1), 127.8 (C_2 or C_3), 123.2 (C_{17}), 67.0 (C_5), 51.3 (C_9), 47.2 (br, C_{10}) 42.8 (C_7), 42.7 (C_7), 36.1 (C_{12}), 35.2 (C_{13}), 33.3 (br, C_8), 32.4 (br, C_8), 20.9 (C_{11}); **IR** ν_{max}/cm^{-1} (neat): 2937, 2856, 1771 (C=O, phthalimide), 1703 (C=O, carboxybenzyl), 1467, 1433, 1396, 1364, 1274, 1225, 1158, 1127, 1088, 1053, 1015; **HRMS** (NSI): calcd. for $C_{25}H_{30}O_4N_3^+$: 436.2231, found 436.2220, Δ 2.5 ppm

N-(4-Phenylbutan-2-yl)cyclohexanamine (**359**)



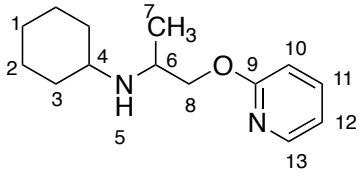
Crude material was prepared using *General Procedure B*, using 4-phenyl-2-butanone (7.4 ml, 50 mmol) and cyclohexylamine (6.9 ml, 60 mmol).

The crude product was purified by Kugelrohr distillation (b.p. ≈ 165 °C, 0.3 mbar) to provide *N*-(4-phenylbutan-2-yl)cyclohexanamine (7.70 g, 30 mmol, 60%) as a colourless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.25 (2H, m, H_{11}), 7.20 – 7.16 (3H, m, H_{12} & H_{13}), 2.82 (1H, app. sextet, *J* = 6.1, H_6), 2.69 – 2.58 (2H, m, H_9), 2.50 (1H, tt, *J* = 10.5, 3.8, H_4), 1.87 – 1.80 (2H, m, H_3), 1.78 – 1.74 (1H, m, H_8), 1.73 – 1.68 (2H, m, H_2), 1.64 – 1.57 (2H, m, H_1 & H_8), 1.30 – 1.19 (2H, m, H_2), 1.15 (1H, qnt, *J* = 12.2, 3.4, H_1), 1.08 (3H, d, *J* = 6.1, H_7), 1.05 – 0.95 (2H, m, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 142.5 (C_{10}), 128.6 (C_{11}), 128.5 (C_{12}), 125.7 (C_{13}), 53.5 (C_4), 49.0 (C_6), 39.2 (C_8), 34.5 (C_3), 34.0 (C_3), 32.5 (C_9), 26.2 (C_1), 25.3 (C_2), 25.2 (C_2), 21.1 (C_7)**;** **IR** ν_{max}/cm^{-1} (neat): 2925, 2849, 1641 (C=C stretch), 1494, 1451, 1368, 1308, 1138, 1034; **HRMS** (NSI): calcd. for $C_{16}H_{26}N^+$: 232.2060, found 232.2059, Δ 0.3 ppm

The observed characterisation data were consistent with literature values.[200]

N-(1-(Pyridin-2-yloxy)propan-2-yl)cyclohexanamine (**360**)

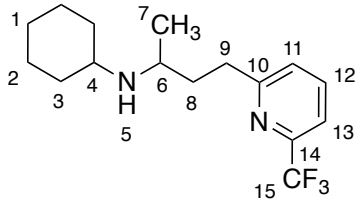


Crude material prepared according to *General Procedure F* using 2-(cyclohexylamino)propan-1-ol (3.15 g, 20 mmol).

The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and further purified by Kugelrohr distillation (b.p. ≈ 140 °C, 0.51 mbar) to provide *N*-(1-(pyridin-2-yloxy)propan-2-yl)cyclohexanamine (2.02 g, 8.6 mmol, 43%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.13 (1H, ddd, *J* = 5.0, 2.0, 0.7, H_{13}), 7.55 (1H, dddd, *J* = 15.5, 9.1, 7.1, 2.0, H_{11}), 6.84 (1H, dddd, *J* = 12.1, 7.1, 5.1, 1.0, H_{12}), 6.73 (1H, dt, *J* = 8.3, 0.9, H_{10}), 4.20 (1H, dd, *J* = 10.3, 4.9, H_8), 4.14 (1H, dd, *J* = 10.3, 6.3, H_8), 3.23 (1H, app. sextet, *J* = 6.6, H_6), 2.56 (1H, tt, *J* = 10.5, 3.8, H_4), 1.92 – 1.85 (2H, m, H_3), 1.74 – 1.68 (2H, m, H_2), 1.62 – 1.57 (1H, m, H_1), 1.30 – 1.14 (3H, m, H_1 & H_2) 1.14 (3H, d, *J* = 6.5, H_7), 1.11 – 0.98 (2H, m, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.9 (C_9), 146.9 (C_{13}), 138.5 (C_{11}), 116.7 (C_{12}), 111.0 (C_{10}), 70.0 (C_8), 53.7 (C_4), 48.6 (C_6), 34.5 (C_3), 33.9 (C_3), 26.2 (C_1), 25.3 (C_2), 25.2 (C_2), 18.4 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2988, 2902, 1594, 1570, 1475, 1450, 1431, 1407, 1394, 1381, 1310, 1284, 1251, 1141, 1066; **HRMS** (NSI): calcd. for $C_{14}H_{23}ON_2^+$: 235.1805, found 235.1805, Δ 0.0 ppm

N-(4-(6-(Trifluoromethyl)pyridin-2-yl)butan-2-yl)cyclohexanamine (**361**)

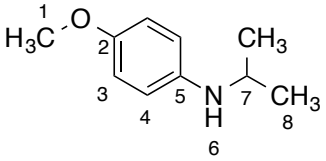


Crude product was prepared according to *General Procedure A* using 4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-one (5.43 g, 25 mmol) and cyclohexylamine (2.9 ml, 25 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 155 °C, 0.5 mbar) to provide *N*-(4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-yl)cyclohexanamine (3.24 g, 11 mmol, 43%) as a clear, colourless liquid.

R_f (10% CH_3OH in CH_2Cl_2): 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.73 (1H, app. t, *J* = 7.8, H_{12}), 7.46 (1H, d, *J* = 7.8, H_{13}), 7.33 (1H, d, *J* = 7.8, H_{11}), 2.89 (2H, t, *J* = 8.0, H_9), 2.80 (1H, app. sextet, *J* = 6.3, H_6), 2.48 (1H, tt, *J* = 10.4, 3.8, H_4), 1.88 – 1.76 (3H, m, H_3 & H_8), 1.74 – 1.65 (3H, m, H_2 & H_8), 1.60 – 1.55 (1H, m, H_1), 1.22 (2H, qnt, *J* = 12.3, 3.4, H_2), 1.13 (1H, qnt, *J* = 12.3, 3.1, H_1), 1.06 (3H, d, *J* = 6.3, H_7), 1.04 – 0.91 (2H, m, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.3 (C_{10}), 147.6 (q, $J_{C\text{-}F}$ = 34.1, C_{14}), 137.4 (C_{12}), 125.5 (C_{11}), 121.7 (q, $J_{C\text{-}F}$ = 274, C_{15}), 117.5 (C_{13}), 53.5 (C_4), 48.8 (C_6), 37.2 (C_8), 34.7 (C_9), 34.5 (C_9), 33.9 (C_3),

26.2 (C_1), 25.3 (C_2), 25.1 (C_2), 21.1 (C_7); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -68.0; **IR** ν_{max}/cm^{-1} (neat): 2927, 2854, 1601, 1463, 1450, 1342, 1257, 1182, 1136, 1092; **HRMS** (NSI): calcd. for $C_{16}H_{24}N_2F_3^+$: 301.1886, found 301.1884, Δ 0.7 ppm

N-Isopropyl-4-methoxyaniline (**250**)



AcOH (12 ml, 200 mmol) was added to a stirred suspension of 4-methoxy-*N*-methylaniline (3.08 g, 25 mmol), acetone (5.0 ml, 68 mmol) and zinc dust (6.54 g, 100 mmol) in CH_3OH (100 ml). The reaction mixture was stirred at rt for 16 h at rt.

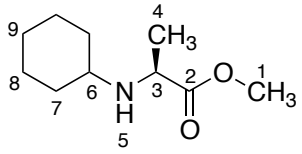
Additional zinc dust (6.54 g, 100 mmol) and AcOH (12 ml, 200 mmol) were then added and the reaction mixture was stirred at rt for a further 18 h. The reaction mixture was filtered through Celite®, washed through with CH_3OH (50 ml) and concentrated under reduced pressure to provide the crude product.

The crude product was purified by Kugelrohr distillation (b.p. ≈ 140 °C, 6 mbar) to provide *N*-isopropyl-4-methoxyaniline (3.27 g, 20 mmol, 79%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.79 (2H, d, *J* = 8.9, H_4), 6.58 (2H, d, *J* = 8.9, H_3), 3.76 (3H, s, H_1), 3.56 (1H, septet, *J* = 6.3, H_7), 3.15 (1H, br s, H_6), 1.20 (6H, d, *J* = 6.3, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.8 (C_2), 141.7 (C_5), 114.8 (C_4), 114.8 (C_3), 55.7 (C_1), 45.1 (C_7), 23.0 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2960, 2823, 1509, 1463, 1404, 1382, 1364, 1294, 1231, 1171, 1038; **HRMS** (NSI): calcd. for $C_{10}H_{16}ON^+$: 166.1226, found 166.1222, Δ 2.7 ppm

The observed characterisation data were consistent with literature values.[201]

Methyl (2S)-2-(cyclohexylamino)propanoate **(251)**

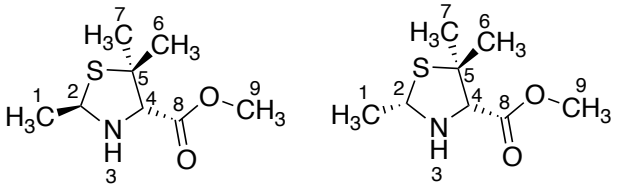


Crude material was prepared by *General Procedure A* using cyclohexanone (6.2 ml, 60 mmol) and alanine methyl ester hydrochloride (6.98 g, 60 mmol). The crude product was purified by flash silica column chromatography eluting with a gradient of 5% CH_3OH in CH_2Cl_2 to 10% CH_3OH in CH_2Cl_2. Fractions containing the product were combined, concentrated under reduced pressure and further purified by Kugelrohr distillation (b.p. ≈ 60 °C, 0.1 mbar) to provide methyl (2S)-2-(cyclohexylamino)propanoate (1.27 g, 6.9 mmol, 46%) as a colourless, clear liquid.

R_f (5% CH_3OH in CH_2Cl_2): 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.72 (3H, s, H_1), 3.50 (1H, q, *J* = 7.0, H_3), 2.35 (1H, tt, *J* = 10.5, 3.6, H_6), 1.87 (1H, br d, *J* = 12.4, H_9), 1.76 – 1.69 (3H, m, H_7 & H_8), 1.61 – 1.57 (2H,

m, H_7 or H_8), 1.28 (3H, d, *J* = 7.0, H_4), 1.24 – 1.08 (3H, m, H_7 & H_8), 1.02 (1H, br qd, *J* = 12.4, 3.3, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.9 (C_2), 55.0 (C_6), 53.4 (C_3), 51.8 (C_1), 34.1 (C_7), 32.9 (C_9), 26.0 (C_8), 25.0 (C_8), 19.8 (C_4); **IR** ν_{max}/cm^{-1} (neat): 2929, 2853, 1736 (C=O stretch), 1449, 1370, 1245, 1193, 1156, 1076, 1054; **HRMS** (APCI): calcd. for $C_{10}H_{20}O_2N^+$: 186.1489, found 186.1488, Δ 0.3 ppm; **$[\alpha]_D^{31}$** = - 38.8° (*c* = 1.0, $CHCl_3$)

(2R,4S)- & (2S,4S)-Methyl 2,5,5-trimethylthiazolidine-4-carboxylate **(254)**



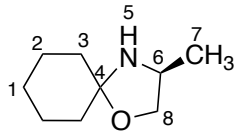
Acetaldehyde (2.3 ml, 41 mmol) was added to a stirred solution of *D*-penicillamine methyl ester hydrochloride (7.50 g, 38 mmol) in CH_3OH (80 ml). The reaction mixture was stirred under nitrogen at rt for 16 h.

The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (200 ml) and washed with sat. aq. $NaHCO_3$ (100 ml). The organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was then purified by flash silica column chromatography eluting with CH_2Cl_2. Fractions containing the diastereomeric mixture of products were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 65 °C, 0.78 mbar) to provide a diastereomeric mixture (3:1 d.r.) of methyl 2,5,5-trimethylthiazolidine-4-carboxylate (3.90 g, 21 mmol, 55%) as a clear, colourless oil.

R_f (CH_2Cl_2): 0.33 (diastereomers coelute); **^{1}H NMR** (400 MHz, d^6-DMSO) δ: 4.81 (1H, dq, *J* = 8.2, 6.4, H_2, minor diastereomer), 4.60 (1H, app. sextet, *J* = 6.2, H_2, major diastereomer), 4.10 (1H, dd, *J* = 12.5, 8.6, H_4, minor diastereomer), 3.70 (3H, s, H_9, major diastereomer), 3.68 (3H, s, H_9, minor diastereomer), 3.40 (1H, t, *J* = 12.8, H_4, major diastereomer), 1.55 (3H, s, H_6, major diastereomer), 1.54 (3H, s, H_6, minor diastereomer), 1.44 (3H, d, *J* = 6.2, H_1, major diastereomer), 1.32 (3H, d, *J* = 6.4, H_1, minor diastereomer), 1.16 (3H, s, H_7, major diastereomer), 1.15 (3H, s, H_7, minor diastereomer); **^{13}C NMR** (100 MHz, d^6-DMSO) δ: 170.0 (C_8, minor diastereomer), 169.6 (C_8, major diastereomer), 74.2 (C_4, major diastereomer), 71.8 (C_4, minor diastereomer), 63.3 (C_2, major diastereomer), 62.1 (C_2, minor diastereomer), 59.6 (C_5, major diastereomer), 59.5 (C_5, minor diastereomer), 51.9 (C_9, both diastereomers), 29.1 (C_7, major diastereomer), 29.0 (C_6, major diastereomer), 28.6 (C_6, minor diastereomer), 27.1 (C_7, minor diastereomer), 26.1 (C_1, minor diastereomer), 20.7 (C_1, major diastereomer); **IR** ν_{max}/cm^{-1} (neat): 3310 (N-H stretch), 2964, 2925, 1738 (C=O stretch), 1453, 1433, 1381, 1366, 1312, 1241, 1205, 1167, 1146, 1128,1084, 1021; **HRMS** (NSI): calcd. for $C_8H_{16}O_2NS^+$: 190.0896, found 190.0898, Δ 0.9 ppm; **$[\alpha]_D^{31}$** = +50.3° (*c* = 1.0, $CHCl_3$)

The observed characterisation data were consistent with literature values.[202]

(*S*)-3-Methyl-1-oxa-4-azaspiro[4.5]decane **(256)**

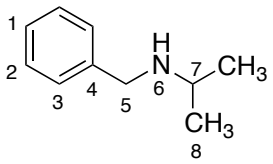


Pyridinium *p*-toluenesulfonate (1.26 g, 5.0 mmol) was added to a stirred solution of cyclohexanone (5.2 ml, 50 mmol) and L-alaninol (4.0 ml, 50 mmol) in toluene (200 ml). The reaction mixture was heated at reflux under Dean Stark conditions for 18 h.

The reaction mixture was cooled to rt, washed with sat. aq. $NaHCO_3$ (2 × 100 ml). The combined aqueous layers were further extracted with EtOAc (2 × 100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation (b.p. ≈ 80 °C, 0.5 mbar) to provide (*S*)-3-methyl-1-oxa-4-azaspiro[4.5]decane (4.98 g, 32 mmol, 64%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (1H, dd, *J* = 7.6, 6.6, H_8), 3.45 (1H, app. sextet, *J* = 6.3, H_6), 3.13 (1H, app. t, *J* = 8.0, H_8), 1.69 – 1.32 (11 H, m, H_1, H_2, H_3 & H_5), 1.21 (3H, d, *J* = 6.3, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 96.5 (C_4), 71.8 (C_8), 53.0 (C_6), 37.7 (C_3), 36.0 (C_3), 25.5 (C_1), 24.0 (C_2), 23.7 (C_2), 18.0 (C_7); **IR** ν_{max}/cm^{-1} (neat): 1448, 1407, 1394, 1372, 1241, 1159, 1116, 1058, 1037; **HRMS** (NSI): calcd. for $C_9H_{18}ON^+$: 156.1383, found 156.1380, Δ 1.9 ppm; **$[\alpha]_D^{26}$** = +48.1° (*c* = 1.0, $CHCl_3$)

N-Benzylpropan-2-amine **(257)**



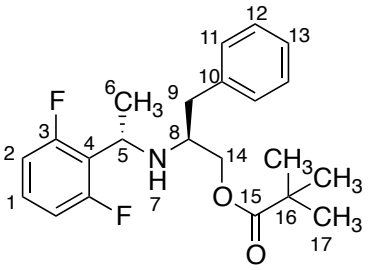
Crude material prepared according to *General Procedure B* using acetone (4.0 ml, 55 mmol), and cyclohexylamine (3.3 ml, 30 mmol).

The crude product was purified by Kugelrohr distillation (b.p. ≈ 95 °C, 6 mbar) to provide *N*-benzylpropan-2-amine (2.74 g, 18 mmol, 61%) as a colourless, clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.20 (5H, m, H_1, H_2 & H_3), 3.98 (2H, s, H_5), 3.10 (1H, septet, *J* = 6.5, H_7), 2.04 (1H, br s, H_6), 1.26 (6H, d, *J* = 6.5, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 133.0 (C_4), 129.6 (C_2), 128.9 (C_3), 125.9 (C_1), 48.3 (C_5), 48.2 (C_7), 19.6 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2988, 2902, 1710, 1605, 1556, 1395, 1251, 1066, 1050, 1010; **HRMS** (NSI): calcd. for $C_{10}H_{16}N_1$: 150.1277, found 150.1273, Δ 2.8 ppm

The observed characterisation data were consistent with literature values.[203]

(S)-2-(((S)-1-(2,6-Difluorophenyl)ethyl)amino)-3-phenylpropyl pivalate **(261)**



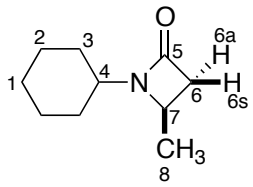
Crude material prepared according to *General Procedure G* using (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropan-1-ol (13.11 g, 45 mmol).

The crude product was purified by flash silica column chromatography eluting with a gradient of 20% EtOAc in petroleum ether b.p 40 – 60 °C. Fractions containing the product were combined, concentrated under reduced pressure and then further purified by Kugelrohr distillation (b.p. ≈ 160 °C, 0.3 mbar) to provide (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropyl pivalate (13.09 g, 35 mmol, 77%) as a clear, colourless liquid

R_f (20% EtOAc in petroleum ether b.p. 40 – 60 °C): 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.20 – 7.16 (3H, m, H_{12} & H_{13}), 7.14 – 7.06 (1H, m, H_1), 6.97 (2H, dd, *J* = 7.3, 3.5, H_{11}), 6.71 (2H, app. t, *J* = 8.7, H_2), 4.34 (1H, q, *J* = 7.0, H_5), 4.14 (1H, dd, *J* = 11.1, 5.0, H_{14}), 3.99 (1H, dd, *J* = 11.1, 5.0, H_{14}), 2.86 – 2.77 (2H, m, H_8 & H_9), 2.51 (1H, dd, *J* = 13.1, 7.9, H_9), 1.78 (1H, br s, H_7), 1.41 (3H, d, *J* = 7.0, H_6), 1.24 (9H, s, H_{17}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.4 (C_{15}), 161.3 (dd, $J_{C\text{-}F}$ = 246.7, 9.1, C_3), 137.8 (C_{10}), 128.9 (C_{11}), 128.5 (C_{12}), 128.1 (t, $J_{C\text{-}F}$ = 10.6, C_1), 126.4 (C_{13}), 120.0 (t, $J_{C\text{-}F}$ = 17.6, C_4), 111.5 (d, $J_{C\text{-}F}$ = 26.6, C_2), 66.2 (C_{14}), 55.9 (C_8), 46.4 (C_5), 38.9 (C_{16}), 38.9 (C_9), 27.3 (C_{17}), 21.2 (C_6); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -115.4; IR ν_{max}/cm^{-1} (neat): 2975, 1728 (C=O stretch), 1622, 1591, 1480, 1470, 1455, 1398, 1366, 1282, 1256, 1230, 1150, 1079, 1032; **HRMS** (NSI): calcd. for $C_{22}H_{28}O_2NF_2^+$: 376.2083, found 376.2088, Δ 1.4 ppm; **$[\alpha]_D^{24}$** = -51.0° (*c* = 1.0, $CHCl_3$)

4.7 Preparation of carbonylation products

1-Cyclohexyl-4-methylazetidin-2-one (**196**)



Crude material prepared according to *General Procedure J* using *N*-cyclohexylisopropylamine (70.6 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), Li-quinoline (5.3 mg, 0.03 mmol) and a 6 h reaction time. The crude product was purified by flash silica column chromatography eluting with 80% Et_2O in hexane, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide 1-cyclohexyl-4-methylazetidin-2-one (68.8 mg, 0.41 mmol, 82%) as a colourless oil.

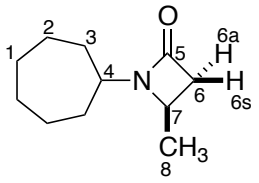
The reaction performed according to *General Procedure H*, followed by flash silica column chromatography eluting with 80% Et_2O in hexane provided 1-cyclohexyl-4-methylazetidin-2-one (62.5 mg, 0.37 mmol, 75%) as a brown oil.

The reaction performed according to *General Procedure I* on a 5 mmol scale followed by flash silica column chromatography eluting with 80% Et_2O in hexane provided 1-cyclohexyl-4-methylazetidin-2-one (646.6 mg, 3.9 mmol, 77%) as a brown oil.

R_f (80% Et_2O/Hexane): 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.71 (1H, qnd, *J* = 6.0, 2.0, H_7), 3.42 (1H, tt, *J* = 11.7, 3.9, H_4), 2.97 (1H, dd, J = 14.4, 5.0, H_{6a}), 2.41 (1H, dd, *J* = 14.4, 2.2, H_{6s}), 1.88 (2H, br t, *J* = 13.2, H_3), 1.77 (2H, br t, *J* = 14.6, H_2), 1.65 – 1.61 (1H, m, H_1), 1.51 (1H, qd, *J* = 12.3, 3.2, H_3), 1.39 (1H, qd, *J* = 12.3, 3.2, H_3), 1.34 (3H, d, *J* = 6.0, H_8), 1.26 (2H, app. tt, *J* = 12.2, 3.2, H_2), 1.14 (1H, app. qnt, *J* = 12.5, 3.2, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3 (C_5), 51.8 (C_4), 46.3 (C_7), 43.3 (C_6), 32.1 (C_3), 30.7 (C_3), 25.4 (C_1), 25.3 (C_2), 20.7 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2933, 2853, 1728 (C=O stretch), 1639, 1449, 1393, 1378, 1364, 1346, 1318, 1262, 1233, 1199, 1126, 1064; **HRMS** (NSI): calcd. for $C_{10}H_{18}ON^+$: 168.1383, found 168.1380, Δ 1.7 ppm

The observed characterisation data were consistent with literature values.[204]

1-Cycloheptyl-4-methylazetidin-2-one (**202**)

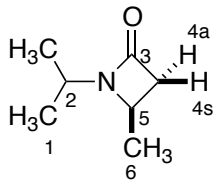


Crude material prepared according to *General Procedure H* using N-isopropylcycloheptylamine (77.6 mg, 0.50 mmol). The crude product was purified by flash silica column chromatography eluting with 80% Et_2O

in petroleum ether b.p. 40 – 60 °C to provide 1-cycloheptyl-4-methylazetidin-2-one (62.4 mg, 0.34 mmol, 69%) as a brown oil.

R_f (80% Et_2O in petroleum ether b.p. 40 – 60 °C): 0.18; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.74 (1H, m, H_7), 3.60 (1H, tt, *J* = 10.2, 4.3, H_4), 2.95 (1H, dd, *J* = 14.3, 5.0, H_{6a}), 2.40 (1H, dd, *J* = 14.3, 2.3, H_{6s}), 1.94 – 1.87 (2H, m, H_3), 1.73 – 1.37 (10 H, m, H_1, H_2, H_3), 1.33 (3H, d, *J* = 6.1, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.9 (C_5), 54.0 (C_4), 46.4 (C_7), 43.2 (C_6), 34.3 (C_3), 32.6 (C_3), 27.8 (C_2), 27.5 (C_2), 24.7 (C_1), 24.6 (C_1), 20.6 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2925, 2857, 1730 (C=O stretch), 1637, 1455, 1380, 1346, 1318, 1237, 1203, 1106, 1066; **HRMS** (APCI): calcd. for $C_{11}H_{20}ON^+$: 182.1539, found 182.1538, Δ 0.8 ppm

1-Isopropyl-4-methylazetidin-2-one **(204)**



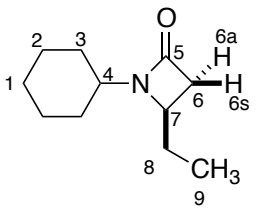
Crude material prepared according to *General Procedure J* using diisopropylamine (50.6 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), Li-quinoline (5.3 mg, 0.03 mmol), a reaction temperature of 100 °C and a reaction time of 6 h. The crude product was purified by flash silica column chromatography eluting with Et_2O, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide 1-isopropyl-4-methylazetidin-2-one (45.0 mg, 0.35 mmol, 71%) as a colourless oil.

The reaction performed according to *General Procedure H* at 100 °C, followed by flash silica column chromatography eluting with Et_2O provided 1-isopropyl-4-methylazetidin-2-one (38.8 mg, 0.31 mmol, 61%) as a brown oil.

R_f (Et_2O): 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.82 (1H, septet, *J* = 6.8, H_2), 3.74 – 3.69 (1H, m, H_5), 2.96 (1H, dd, *J* = 14.3, 5.0, H_{4a}), 2.41 (1H, dd, *J* = 14.3, 2.2, H_{4s}), 1.35 (3H, d, *J* = 6.1, H_6), 1.25 (3H, d, *J* = 6.8, H_1), 1.21 (3H, d, *J* = 6.8, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3 (C_3), 46.1 (C_5), 43.8 (C_2), 43.3 (C_4), 21.9 (C_1), 20.7 (C_6), 20.1 (C_1); **IR** ν_{max}/cm^{-1} (neat): 2969, 1729 (C=O stretch), 1380, 1243, 1209, 1066, 1044; **HRMS** (NSI): calcd. for $C_7H_{13}ONNa^+$: 150.0889, found 150.0888, Δ 0.9 ppm

The observed characterisation data were consistent with literature values.[156]

1-Cyclohexyl-4-ethylazetidin-2-one (**205**)

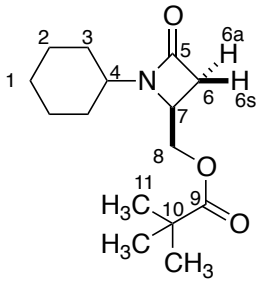


Crude material prepared according to *General Procedure J* using *N*-(*sec*-butyl)cyclohexanamine (77.6 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol) and Li-quinoline (5.3 mg, 0.03 mmol) for 6 h. The crude product was purified by flash silica column chromatography eluting with 60% Et_2O in hexane, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide 1-cyclohexyl-4-ethylazetidin-2-one (55.4 mg, 0.31 mmol, 61%) as a colourless oil.

The reaction performed according to *General Procedure H* followed by flash silica column chromatography eluting with 60% Et_2O in hexane provided 1-cyclohexyl-4-ethylazetidin-2-one (45.3 mg, 0.25 mmol, 50%) as a brown oil.

R_f (60% Et_2O in hexane): 0.14; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.61 – 3.56 (1H, m, H_7), 3.42 (1H, tt, J = 11.8, 3.8, H_4), 2.92 (1H, dd, J = 14.5, 4.9, H_{6a}), 2.49 (1H, dd, J = 14.7, 2.1, H_{6s}), 1.96 – 1.85 (3H, m, H_3 & H_8), 1.82 – 1.72 (2H, m, H_2), 1.67 – 1.60 (1H, m, H_1), 1.60 – 1.37 (3H, m, H_3 & H_8), 1.35 – 1.22 (2H, m, H_2), 1.15 (1H, qnt, J = 12.6, 3.4, H_1), 0.92 (3H, t, J = 7.4, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.8 (C_5), 52.0 (C_4), 51.9 (C_7), 40.7 (C_6), 32.2 (C_3), 30.6 (C_3), 27.2 (C_8), 25.4 (C_1), 25.3 (C_2), 9.2 (C_9); **IR** ν_{max}/cm^{-1} (neat): 2929, 2855, 1735 (C=O stretch), 1451, 1391, 1366; **HRMS** (NSI): calcd. for $C_{11}H_{20}ON^+$: 182.1539, found 182.1536, Δ 1.9 ppm

(1-Cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (**206**)



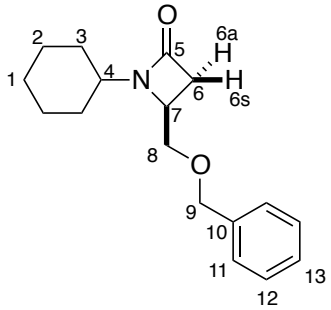
Crude material prepared according to *General Procedure J* using 2-(cyclohexylamino)propyl pivalate (120.7 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with 50% EtOAc in hexane, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide (1-cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (86.7 mg, 0.32 mmol, 65%) as a colourless oil.

The reaction performed according to *General Procedure H* followed by flash silica column chromatography eluting with 50% EtOAc in hexane provided (1-cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (73.5 mg, 0.28 mmol, 55%) as a brown oil.

R_f (50% EtOAc/hexane): 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.30 (1H, dd, *J* = 12.0, 3.8, H_8), 4.13 (1H, dd, *J* = 12.1, 5.1, H_8), 3.87 – 3.83 (1H, m, H_7), 3.42 (1H, tt, *J* = 11.8, 3.8, H_4), 2.95 (1H, dd, *J* = 14.5, 5.3, H_{6a}), 2.65 (1H, dd, *J* = 14.5, 2.4, H_{6s}), 1.92 – 1.84 (2H, m, H_3), 1.82 – 1.73 (2H, m, H_2), 1.65 – 1.61 (1H, m, H_1), 1.59 (1H, qd, *J* = 12.6, 3.8, H_3), 1.41 (1H, qd, *J* = 12.2, 3.6, H_3), 1.32 – 1.24 (1H, m, H_2), 1.22 (9H, s, H_{11}), 1.21 – 1.19 (1H, m, H_2), 1.15 (1H, qnt, *J* = 12.8, 3.5, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.1

(C_9), 165.9 (C_5), 64.6 (C_8), 52.4 (C_4), 48.6 (C_7), 38.6 (C_6), 31.9 (C_3), 30.5 (C_3), 27.2 (C_{11}), 25.3 (C_1), 25.2 (C_2), 25.2 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2934, 2858, 1728 (C=O stretch, lactam), 1481, 1452, 1397, 1365, 1281, 1221, 1120, 1145, 1078, 1052, 1035; **HRMS** (NSI): calcd. for $C_{15}H_{26}O_3N^+$: 268.1907, found 268.1907, Δ 0.1 ppm

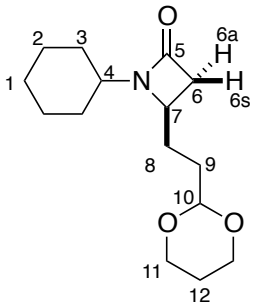
4-((Benzyloxy)methyl)-1-cyclohexylazetidin-2-one (**208**)



Crude material prepared according to *General Procedure H* using *N*-(1-(benzyloxy)propan-2-yl)cyclohexanamine (123.7 mg, 0.50 mmol). The crude product was purified by flash silica column chromatography eluting with 30% EtOAc in hexane to provide 4-((benzyloxy)methyl)-1-cyclohexylazetidin-2-one (65.5 mg, 0.24 mmol, 48%) as a brown oil.

R_f (30% EtOAc in hexane): 0.12; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 – 7.29 (5H, m, H_{11}, H_{12}, H_{13}), 4.54 (2H, s, H_9), 3.83 – 3.79 (1H, m, H_7), 3.60 (1H, dd, *J* = 9.7, 4.3, H_8), 3.56 (1H, dd, *J* = 9.7, 6.2, H_8), 3.45 (1H, tt, *J* = 11.8, 3.8, H_4), 2.90 (1H, dd, *J* = 14.3, 5.2, H_{6a}), 2.57 (1H, dd, *J* = 14.3, 2.4, H_{6s}), 1.87 – 1.69 (4H, m, H_2 & H_3), 1.63 – 1.57 (2H, m, H_1 & H_3), 1.44 (1H, qd, *J* = 12.4, 3.6, H_3), 1.30 – 1.17 (2H, m, H_2), 1.10 (1H, tt, *J* = 12.5, 3.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3 (C_5), 137.6 (C_{10}), 128.5 (C_{12}), 127.9 (C_{13}), 127.7 (C_{11}), 73.5 (C_9), 72.4 (C_8), 52.3 (C_4), 49.7 (C_7), 38.9 (C_6), 31.9 (C_3), 30.4 (C_3), 25.4 (C_2), 25.3 (C_2), 25.3 (C_1); **IR** ν_{max}/cm^{-1} (neat): 2931, 2855, 1740 (C=O stretch, lactam), 1497, 1452, 1392, 1366, 1312, 1260, 1198, 1097, 1028; **HRMS** (NSI): calcd. for $C_{17}H_{24}O_2N^+$: 274.1802, found 274.1803, Δ 0.5 ppm

4-(2-(1,3-Dioxan-2-yl)ethyl)-1-cyclohexylazetidin-2-one (**213**)



Crude material prepared according to *General Procedure J* using *N*-(4-(1,3-dioxan-2-yl)butan-2-yl)cyclohexanamine (120.6 mg, 0.50 mmol) and Li_2CO_3 (74 mg, 1.0 mmol) for 6 h. The crude product was purified by flash silica column chromatography eluting with 60% EtOAc in hexane, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to

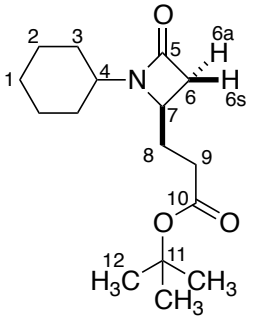
provide 4-(2-(1,3-dioxan-2-yl)ethyl)-1-cyclohexylazetidin-2-one (83.7 mg, 0.31 mmol, 63%) as a colourless oil.

The reaction performed according to *General Procedure H* followed by flash silica column chromatography eluting with 60% EtOAc in hexane provided (1-cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (38.8 mg, 0.15 mmol, 29%) as a brown oil.

The reaction performed according to *General Procedure H* with added Li_2CO_3 (74 mg) followed by flash silica column chromatography eluting with 60% EtOAc in hexane provided (1-cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (48.1 mg, 0.18 mmol, 36%) as a brown oil.

R_f (60% EtOAc/hexane): 0.13; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.53 (1H, t, *J* = 4.8, H_{10}), 4.09 (1H, dd, *J* = 11.7, 4.9, H_{11}), 3.74 (2H, td, *J* = 12.2, 2.5, H_{11}), 3.60 – 3.55 (1H, m, H_7), 3.38 (1H tt, *J* = 11.9, 3.9, H_4), 2.88 (1H, dd, *J* = 14.4, 4.9, H_{6a}), 2.45 (1H, dd, *J* = 14.4, 2.2, H_{6s}), 2.11 – 1.94 (2H, m, H_9 & H_{12}), 1.90 – 1.82 (2H, m, H_3), 1.79 - 1.73 (2H, m, H_2), 1.64 – 1.46 (5H, m, H_2, H_3, H_8, & H_9), 1.42 – 1.31 (2H, m, H_3 & H_{12}), 1.30 – 1.21 (2H, m, H_1 & H_2), 1.14 (1H, tt, *J* = 12.5, 3.4, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.4 (C_5), 101.4 (C_{10}), 66.9 (C_{11}), 52.1 (C_4), 50.4 (C_7), 41.4 (C_6), 32.2 (C_3), 31.1 (C_8), 30.7 (C_3), 28.6 (C_9), 25.7 (C_{12}), 25.3 (C_1), 25.3 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2929, 2854, 1735 (C=O stretch), 1397, 1374, 1238, 1142 (C-O stretch); **HRMS** (NSI): calcd. for $C_{15}H_{26}O_3N^+$: 268.1907, found 268.1908, Δ 0.3 ppm

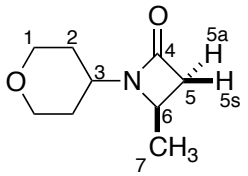
tert-Butyl 3-(1-cyclohexyl-4-oxoazetidin-2-yl)propanoate **(212)**



Crude material prepared according to *General Procedure H* using *tert*-butyl 4-(cyclohexylamino)pentanoate (127.7 mg, 0.50 mmol). The crude product was purified by flash silica column chromatography eluting with 20% EtOAc in hexane to provide *tert*-butyl 3-(1-cyclohexyl-4-oxoazetidin-2-yl)propanoate (23.6 mg, 0.08 mmol, 17%) as a brown oil.

R_f (20% EtOAc in hexane): 0.11; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.64 – 3.59 (1H, m, H_7), 3.40 (1H, tt, *J* = 12.0, 3.8, H_4), 2.89 (1H, dd, *J* = 14.4, 5.0, H_{6a}), 2.44 (1H, dd, *J* = 14.4, 2.3, H_{6s}), 2.29 – 2.15 (2H, m, H_9), 1.91 – 1.82 (2H, m, H_3), 1.80 – 1.60 (5H, m, H_2, H_1, H_8), 1.54 (1H, qd, *J* = 12.0, 3.8, H_3), 1.44 (9H, s, H_{12}), 1.35 – 1.07 (4H, m, H_3, H_2 & H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.9 (C_{10}), 166.2 (C_5), 80.8 (C_{11}), 52.1 (C_4), 49.8 (C_7), 41.1 (C_6), 36.4 (C_8), 32.2 (C_3), 31.3 (C_9), 30.6 (C_3), 29.4 (C_2), 28.1 (C_{12}), 25.3 (C_1), 25.3 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2980, 2912, 1732 (C=O stretch, lactam), 1676 (C=O stretch, ester), 1451, 1411, 1376, 1248, 1075, 1054; **HRMS** (NSI): calcd. for $C_{11}H_{20}ON^+$ [M - $CO_2{}^t$Bu]: 182.1539, found 182.1536, Δ 1.9 ppm

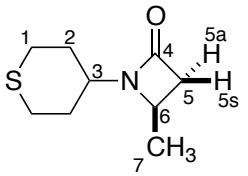
4-Methyl-1-(tetrahydro-2H-pyran-4-yl)azetidin-2-one (**214**)



Crude material prepared according to *General Procedure J* using *N*-isopropyltetrahydro-2*H*-pyran-4-amine (71.6 mg, 0.50 mmol) for 6 h. The crude product was purified by flash silica column chromatography eluting with EtOAc, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide 4-methyl-1-(tetrahydro-2*H*-pyran-4-yl)azetidin-2-one (63.5 mg, 0.38 mmol, 75%) as a colourless oil.

R_f (EtOAc): 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.02 – 3.95 (2H, m, H_1), 3.78 – 3.72 (1H, m, H_6), 3.71 (1H, tt, *J* = 11.5, 4.3, H_3), 3.40 (2H, qd, *J* = 11.7, 2.5, H_1), 3.01 (1H, dd, J = 14.5, 5.0, H_{5a}), 2.45 (1H, dd, *J* = 14.5, 2.3, H_{5s}), 1.92 – 1.71 (4H, m, H_2), 1.37 (3H, d, *J* = 6.1, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.5 (C_4), 66.9 (C_1), 66.9 (C_1), 48.8 (C_3), 46.5 (C_6), 43.5 (C_5), 32.0 (C_2), 30.5 (C_2), 20.8 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2952, 2845, 1730 (C=O stretch), 1381, 1366, 1348, 1237, 1200, 1142, 1088, 1015; **HRMS** (NSI): calcd. for $C_9H_{16}N^+$: 170.1176, found 170.1173, Δ 1.5 ppm

4-Methyl-1-(tetrahydro-2H-thiopyran-4-yl)azetidin-2-one (**215**)

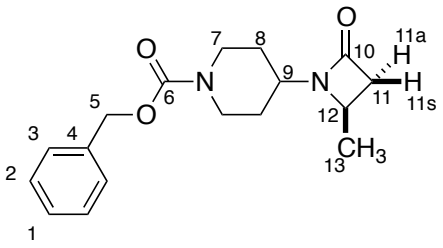


N-Isopropyltetrahydro-2*H*-thiopyran-4-amine was prepared by Dr Darren Willcox according to the procedure published in *Science*[129]

The crude β-lactam was prepared by *General Procedure J* using *N*-isopropyltetrahydro-2*H*-thiopyran-4-amine (79.6 mg, 0.5 mmol) for 6 h. The crude product was purified by flash silica column chromatography eluting with 80% EtOAc in hexane, the combined fractions were passed through a plug of charcoal eluting with Et_2O and concentrated under reduced pressure to provide 4-methyl-1-(tetrahydro-2*H*-thiopyran-4-yl)azetidin-2-one (68.2 mg, 0.37 mmol, 74%) as a colourless oil.

R_f (80% EtOAc in hexane): 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.76 – 3.71 (1H, m, H_6), 3.49 (1H, tt, *J* = 11.9, 3.6, H_3), 2.98 (1H, dd, *J* = 14.6, 5.1, H_{5a}), 2.73 – 2.58 (4H, m, H_1), 2.42 (1H, dd, *J* = 14.6, 2.2, H_{5s}), 2.18 – 2.10 (2H, m, H_2), 1.88 (1H, qd, *J* = 11.6, 4.2, H_2), 1.77 (1H, qd, *J* = 11.9, 3.8, H_2), 1.35 (3H, d, *J* = 6.1, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.2 (C_4), 50.8 (C_3), 46.5 (C_6), 43.5 (C_5), 33.4 (C_2), 31.8 (C_2), 28.1 (C_1), 28.0 (C_1), 20.8 (C_7); **IR** ν_{max}/cm^{-1} (neat): 2914, 1728 (C=O stretch, lactam), 1638, 1380, 1364, 1316, 1270, 1215, 1190, 1109, 1072, 1044; **HRMS** (NSI): calcd. for $C_9H_{16}ONS^+$: 186.0947, found 186.0944, Δ 1.7 ppm

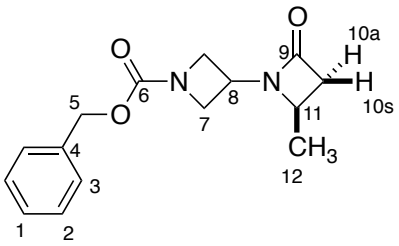
Benzyl 4-(2-methyl-4-oxoazetidin-1-yl)piperidine-1-carboxylate (**198**)



Crude material prepared according to *General Procedure J* using benzyl 4-(isopropylamino)piperidine-1-carboxylate (138.2 mg, 0.50 mmol), 1,4-benzoquinone (108.2 mg, 1.0 mmol) and a 16 h reaction time. The crude product was purified by flash silica column chromatography eluting with EtOAc and concentrated under reduced pressure to provide benzyl 4-(2-methyl-4-oxoazetidin-1-yl)piperidine-1-carboxylate (125.7 mg, 0.42 mmol, 83%) as a light brown oil.
The reaction performed according to *General Procedure H* for 24 h, followed by flash silica column chromatography eluting with EtOAc provided benzyl 4-(2-methyl-4-oxoazetidin-1-yl)piperidine-1-carboxylate (109.8 mg, 0.36 mmol, 77%) as a light brown oil.

R_f (EtOAc): 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.37 – 7.28 (5H, m, H_1, H_2 & H_3), 5.11 (2H, s, H_5), 4.18 (2H, br s, H_7), 3.71 (1H, app. qnd, *J* = 6.0, 2.2, H_{12}), 3.61 (1H, tt, *J* = 11.6, 4.2, H_9), 2.99 (1H, dd, *J* = 14.6, 5.2, H_{11a}), 2.90 – 2.74 (2H, m, H_7), 2.44 (1H, dd, *J* = 14.6, 2.2, H_{11s}), 1.89 – 1.80 (2H, m, H_8), 1.73 (1H, qd, *J* = 7.2, 4.2, H_8), 1.59 (1H, br qd, *J* = 12.2, 4.2, H_8), 1.33 (3H, d, *J* = 6.0, H_{13}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.5 (C_{10}), 155.1 (C_6), 136.7 (C_4), 128.5 (C_2), 128.1 (C_1), 127.9 (C_3), 67.2 (C_5), 49.8 (C_9), 46.6 (C_{12}), 43.5 (C_{11}), 43.0 (C_7), 30.9 (C_8), 29.6 (C_8), 20.7 (C_{13}); **IR** ν_{max}/cm^{-1} (neat): 2972, 2900, 1738 (C=O stretch, lactam), 1694 (C=O stretch, carboxybenzyl), 1408, 1227, 1062; **HRMS** (NSI): calcd. for $C_{17}H_{23}O_3N_2^+$: 303.1706, found 303.1703, Δ 0.9 ppm

Benzyl 2-methyl-4-oxo-[1,3'-biazetidine]-1'-carboxylate (**216**)

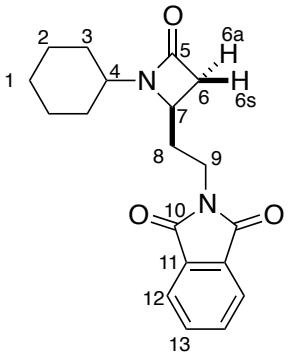


Crude material prepared according to *General Procedure J* using benzyl 3-(isopropylamino)azetidine-1-carboxylate (124.2 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with EtOAc and concentrated under reduced pressure to provide benzyl 2-methyl-4-oxo-[1,3'-biazetidine]-1'-carboxylate (75.0 mg, 0.27 mmol, 55%) as a brown oil.

R_f (EtOAc): 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 – 7.30 (5H, m, H_1, H_2 & H_3), 5.10 (2H, s, H_5), 4.48 (1H, br qn, *J* = 6.8, H_8), 4.26 – 4.20 (3H, m, H_7), 4.13 (1H, dd, *J* = 9.2, 5.7, H_7), 3.87 (1H, qnd, *J* = 5.6, 2.4, H_{11}), 3.07 (1H, dd, *J* = 14.7, 5.1, H_{10a}), 2.54 (1H, dd, *J* = 14.8, 2.4, H_{10s}), 1.44 (3H, d, *J* = 6.3, H_{12}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.8 (C_9), 156.2 (C_6), 136.4 (C_4), 128.5 (C_2), 128.2 (C_1) 128.1 (C_3), 66.9 (C_5), 55.3 (C_7), 53.4 (C_7), 47.4 (C_{11}), 43.8 (C_{10}). 41.1 (C_8), 20.2 (C_{12}); **IR** ν_{max}/cm^{-1} (neat): 1740 (C=O,

lactam) 1703 (C=O, carboxybenzyl), 1416, 1351, 1228; **HRMS** (NSI): calcd. for $C_{15}H_{19}O_3N_2^+$: 275.1390, found 275.1392, Δ 0.7 ppm

2-(2-(1-Cyclohexyl-4-oxoazetidin-2-yl)ethyl)isoindoline-1,3-dione (**199**)

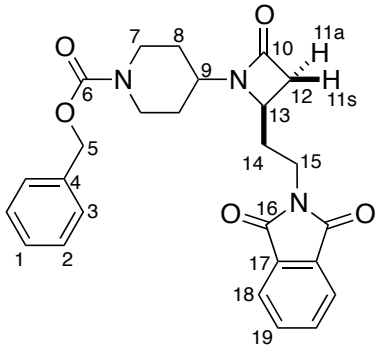


Crude material prepared by *General Procedure J* using 2-(3-(cyclohexylamino)butyl)isoindoline-1,3-dione (150.2 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with 50% EtOAc in hexane and concentrated under reduced pressure to provide 2-(2-(1-cyclohexyl-4-oxoazetidin-2-yl)ethyl)isoindoline-1,3-dione (117.6 mg, 0.36 mmol, 72%) as a light brown oil.

The reaction performed according to *General Procedure H* followed by flash silica column chromatography eluting with 50% EtOAc in hexane provided 2-(2-(1-cyclohexyl-4-oxoazetidin-2-yl)ethyl)isoindoline-1,3-dione (97.5 mg, 0.30 mmol, 59%) as a brown oil.

R_f (50% EtOAc/hexane): 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (2H, dd, *J* = 5.4, 3.1, H_{13}), 7.74 (2H, dd, *J* = 5.5, 3.0, H_{12}), 3.74 (2H, dd, *J* = 6.4, 3.0, H_9), 3.66 – 3.62 (1H, m, H_7), 3.39 (1H, tt, *J* = 11.9, 3.8, H_4), 2.98 (1H, dd, *J* = 14.5, 4.9, H_{6a}), 2.58 (1H, dd, *J* = 14.5, 2.3, H_{6s}), 2.29 (1H, dtd, *J* = 13.6, 7.3, 3.5, H_8), 1.92 – 1.71 (5H, m, H_8, H_3, H_2), 1.64 – 1.59 (1H, m, H_1), 1.53 (1H, qd, *J* = 12.5, 3.7, H_3), 1.40 (1H, qd, *J* = 12.2, 3.5, H_3), 1.24 (2H, qnt, *J* = 12.5, 3.2, H_2), 1.13 (1H, tt, *J* = 12.7, 3.5, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.2 (C_{10}), 166.1 (C_5), 134.2 (C_{12}), 131.9 (C_{11}), 123.4 (C_{13}), 52.2 (C_4), 48.6 (C_7), 41.6 (C_6), 34.5 (C_9), 33.4 (C_8), 32.2 (C_3), 30.7 (C_3), 25.3 (C_1), 25.2 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2984, 2912, 1738 (C=O stretch, lactam), 1706 (C=O stretch, phthalimide), 1451, 1433, 1396, 1378, 1256, 1229, 1072, 1054; **HRMS** (NSI): calcd. for $C_{19}H_{23}O_3N_2^+$: 327.1703, found 327.1701, Δ 0.7 ppm

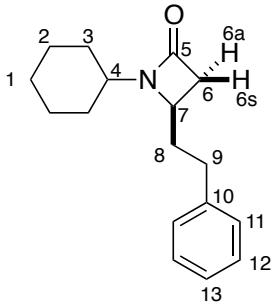
Benzyl 4-(2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-oxoazetidin-1-yl)piperidine-1-carboxylate (**217**)



Crude material prepared according to *General Procedure J* using (*S*)-benzyl 4-((4-(1,3-dioxoisoindolin-2-yl)butan-2-yl)amino)piperidine-1-carboxylate (217.8 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with 80% EtOAc in hexane and concentrated under reduced pressure to provide benzyl 4-(2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-oxoazetidin-1-yl)piperidine-1-carboxylate (156.7 mg, 0.34 mmol, 68%) as a brown oil.

R_f (80% EtOAc/hexane): 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.85 (2H, dd, *J* = 5.4, 3.1, H_{19}), 7.74 (2H, dd, *J* = 5.4, 3.1, H_{18}), 7.37 – 7.28 (5H, m, H_1, H_2, & H_3), 5.10 (2H, s, H_5), 4.18 (2H, br s, H_7), 3.76 – 3.69 (2H, m, H_{15}), 3.68 – 3.63 (1H, m, H_{13}), 3.60 – 3.54 (1H, br m, H_9), 3.02 (1H, dd, *J* = 14.7, 5.0, H_{11a}), 2.86 – 2.73 (2H, m, H_7), 2.61 (1H, dd, *J* = 14.7, 2.3, H_{11s}), 2.28 – 2.22 (1H, m, H_{14}), 1.88 – 1.71 (4H, m, H_8 & H_{14}), 1.61 (1H, qd, *J* = 12.2, 4.2, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.1 (C_{16}), 166.2 (C_{10}), 155.0 (C_6), 136.6 (C_4), 134.2 (C_{18}), 131.9 (C_{17}), 128.5 (C_2), 128.0 (C_3), 127.9 (C_1), 123.4 (C_{19}), 67.2 (C_5), 50.3 (C_9), 48.8 (C_{13}), 43.0 (C_7), 41.8 (C_{12}), 34.4 (C_{15}), 33.3 (C_{14}), 30.9 (br C_8), 29.7 (C_8); **IR** ν_{max}/cm^{-1} (neat): 1772 (C=O stretch, phthalimide), 1737 (C=O stretch, lactam), 1708 (C=O stretch carboxybenzyl), 1435, 1397, 1365, 1275, 1236, 1015; **HRMS** (NSI): calcd. for $C_{26}H_{28}O_5N_3^+$: 462.2023, found 462.2014, Δ 2.0 ppm

1-Cyclohexyl-4-phenethylazetidin-2-one (**218**)



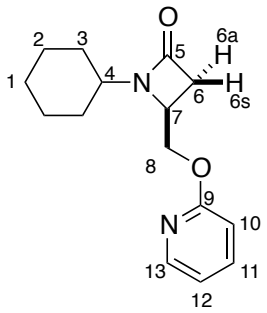
Crude material prepared according to *General Procedure J* using *N*-(4-phenylbutan-2-yl)cyclohexanamine (115.7 mg, 0.50 mmol) for 6 h. The crude product was purified by flash silica column chromatography eluting with 40% EtOAc in hexane and concentrated under reduced pressure to provide 1-cyclohexyl-4-phenethylazetidin-2-one (107.6 mg, 0.42 mmol, 84%) as a light brown oil.

The reaction performed according to *General Procedure H* followed by flash silica column chromatography eluting with 40% EtOAc in hexane provided 1-cyclohexyl-4-phenethylazetidin-2-one (106.4 mg, 0.41 mmol, 83%) as a light brown oil.

R_f (40% EtOAc/hexane): 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 – 7.28 (2H, m, H_{12}), 7.23 – 7.16 (3H, m, H_{11} & H_{13}), 3.65 – 3.60 (1H, m, H_7), 3.40 (1H, tt, *J* = 12.0, 3.9, H_4), 2.92 (1H, dd, *J* = 14.4, 4.8, H_{6a}), 2.70 – 2.56 (2H, m, H_9), 2.49 (1H, dd, *J* = 14.4, 2.3, H_{6s}), 2.26 – 2.17 (1H, m, H_8), 1.91 – 1.82 (2H, m, H_3), 1.81 – 1.70 (3H, m, H_2 & H_8), 1.65 – 1.59 (1H, m, H_1), 1.53 (1H, qd, *J* = 12.3, 3.6, H_3), 1.40 (1H, qd, *J* = 12.1, 3.4, H_3), 1.32 – 1.21 (2H, m, H_2), 1.14 (1H, qnt, *J* = 12.6, 3.5, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.4 (C_5), 140.9 (C_{10}), 128.6 (C_{12}), 128.2 (C_{11}), 126.2 (C_{13}), 52.1 (C_4), 50.4 (C_7), 41.5 (C_6), 36.2 (C_8), 32.3 (C_3), 31.9 (C_9), 30.7 (C_3), 25.4 (C_1), 25.3 (C_2), 25.3 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2929, 2857, 1734 (C=O

stretch), 1635, 1604, 1496, 1453, 1395, 1368, 1318, 1269, 1227, 1199, 1136, 1104, 1076, 1029; **HRMS** (NSI): calcd. for $C_{17}H_{24}ON^+$: 258.1852, found 258.1854, Δ 0.6 ppm

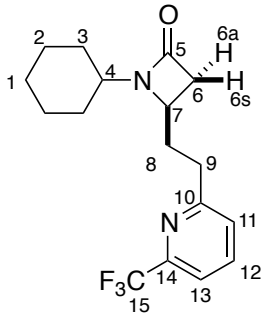
1-Cyclohexyl-4-((pyridin-2-yloxy)methyl)azetidin-2-one (**219**)



Crude material prepared according to *General Procedure J* using *N*-(1-(pyridin-2-yloxy)propan-2-yl)cyclohexanamine (117.2 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with 50% EtOAc in hexane and concentrated under reduced pressure to provide 1-cyclohexyl-4-((pyridin-2-yloxy)methyl)azetidin-2-one (90.2 mg, 0.35 mmol, 69%) as a light brown oil.

R_f (50% EtOAc/hexane): 0.13; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.15 (1H, ddd, *J* = 5.1, 2.0, 0.8, H_{13}), 7.60 (1H, ddd, *J* = 9.0, 7.1, 2.0, H_{11}), 6.91 (1H, ddd, *J* = 7.1, 5.1, 0.9, H_{12}), 6.77 (1H, dt, *J* = 8.3, 0.9, H_{10}), 4.50 (1H, dd, *J* = 11.4, 4.3, H_8), 4.39 (1H, dd, J = 11.4, 5.9, H_8), 4.03 – 3.99 (1H, m, H_7), 3.51 (1H, tt, J = 11.8, 3.8, H_4), 3.00 (1H, dd, *J* = 14.5, 5.3, H_{6a}), 2.74 (1H, dd, *J* = 14.5, 5.3, H_{6s}), 1.93 – 1.83 (2H, m, H_3), 1.81 – 1.76 (1H, m, H_2), 1.75 – 1.69 (1H, m, H_1), 1.64 – 1.59 (2H, m, H_2 & H_3), 1.43 (1H, qd, *J* = 12.4, 3.6, H_3), 1.32 – 1.20 (2H, m, H_2 & H_1), 1.13 (1H, tt, *J* = 12.7, 3.4, H_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3 (C_5), 163.1 (C_9), 146.8 (C_{13}), 138.9 (C_{11}), 117.3 (C_{12}), 111.1 (C_{10}), 66.8 (C_8), 52.2 (C_4), 49.1 (C_7), 39.0 (C_6), 32.0 (C_3), 30.4 (C_3), 25.4 (C_1), 25.3 (C_2); **IR** ν_{max}/cm^{-1} (neat): 2927, 1738 (C=O stretch), 1594, 1571, 1474, 1432, 1394, 1365, 1309, 1273, 1243, 1142 (C-O stretch), 1044, 1019; **HRMS** (NSI): calcd. for $C_{15}H_{21}O_2N_2^+$: 261.1598, found 261.1599, Δ 0.6 ppm

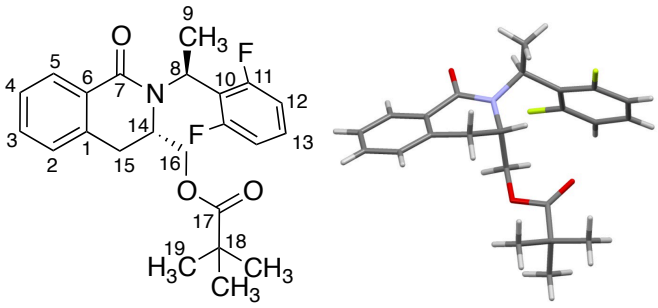
1-Cyclohexyl-4-(2-(6-(trifluoromethyl)pyridin-2-yl)ethyl)azetidin-2-one (**220**)



Crude material prepared according to *General Procedure J* using *N*-(4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-yl)cyclohexanamine (150.2 mg, 0.50 mmol) and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with 50% EtOAc in hexane and concentrated under reduced pressure to provide 1-cyclohexyl-4-(2-(6-(trifluoromethyl)pyridin-2-yl)ethyl)azetidin-2-one (117.7 mg, 0.36 mmol, 72%) as a brown oil.

R_f (50% EtOAc/hexane): 0.11; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (1H, t, *J* = 7.8, H_{12}), 7.53 (1H, d, *J* = 7.8, H_{13}), 7.34 (1H, d, *J* = 7.8, H_{11}), 3.71 – 3.66 (1H, m, H_7), 3.41 (1H, tt, *J* = 11.8, 3.8, H_4), 2.95 – 2.82 (3H, m, H_{6a} & H_9), 2.48 (1H, dd, *J* = 14.4, 2.3, H_{6s}), 2.49 – 2.40 (1H, m, H_8), 1.92 – 1.71 (5H, m, H_2, H_3 & H_8), 1.65 – 1.59 (1H, m, H_1), 1.56 (1H, qd, *J* = 12.4, 3.6, H_3), 1.42 (1H, qd, *J* = 12.1, 3.4, H_3), 1.32 – 1.21 (2H, m, H_2), 1.14 (1H, qnt, *J* = 12.5, 3.3, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3 (C_1), 161.5 (C_{10}), 147.9 (q, $J_{C\text{-}F}$ = 34.5, C_{14}), 137.8 (C_{12}), 125.6 (C_{11}), 121.5 (q, $J_{C\text{-}F}$ = 275, C_{15}), 118.1 (q, $J_{C\text{-}F}$ = 3.0, C_{13}), 52.1 (C_4), 50.0 (C_7), 41.4 (C_6), 33.7 (C_9), 33.6 (C_8), 32.3 (C_3), 30.6 (C_3), 25.3 (C_1 or C_2), 25.3 (C_1 or C_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -68.1; **IR** ν_{max}/cm^{-1} (neat): 2933, 2857, 1733 (C=O stretch, lactam), 1601, 1464, 1396, 1337, 1182, 1136, 1094; **HRMS** (NSI): calcd. for $C_{17}H_{22}ON_2F_3^+$: 327.1679, found 327.1680, Δ 0.4 ppm

((S)-2-((S)-1-(2,6-Difluorophenyl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl pivalate (**262**)



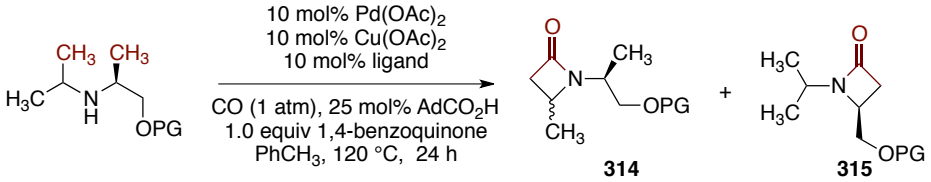
Crude material prepared according to *General Procedure J* using (*S*)-2-(((*S*)-1-(2,6-difluorophenyl)ethyl)amino)-3-phenylpropyl pivalate (187.7 mg, 0.50 mmol), 4-chlorobenzoic acid (19.6 mg, 0.13 mmol) instead of 1-adamantanecarboxylic acid, pyridine (4.0 µL, 0.05 mmol) instead of Li-Quinoline and 1,4-benzoquinone (108.2 mg, 1.0 mmol) for 16 h. The crude product was purified by flash silica column chromatography eluting with a gradient of 5% EtOAc in hexane to 10% EtOAc in hexane, the combined fractions were concentrated under reduced pressure and purified by alumina column chromatography eluting with 10% EtOAc in hexane to provide ((*S*)-2-((*S*)-1-(2,6-difluorophenyl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl pivalate (116.2 mg, 0.29 mmol, 58%) as a white solid.

R_f (10% EtOAc/hexane): 0.08; **m.p.** 98 – 100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.06 (1H, d, *J* = 7.7, H_5), 7.40 (1H, td, *J* = 7.4, 1.4, H_3), 7.32 (1H, br t, *J* = 7.5, H_4), 7.29 - 7.24 (1H, m, H_{13}), 7.12 (1H, br d, *J* = 7.5, H_2), 6.91 (2H, t, *J* = 8.7, H_{12}), 6.22 (1H, q, *J* = 7.1, H_8), 4.17 – 4.12 (1H, m, H_{14}), 3.54 (1H, dd, *J* = 11.0, 9.4, H_{16}), 3.40 (1H, dd, *J* = 11.0, 3.7, H_{16}), 3.30 (1H, dd, *J* = 16.0, 5.6, H_{15}), 2.91 (1H d, *J* = 16.1, H_{15}), 1.80 (3H, dt, *J* = 7.3, 2.4, H_9), 1.06 (9H, s, H_{19}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.5 (C_{17}), 162.4 (d, $J_{C\text{-}F}$ = 250.4, 8.2, C_{11}), 163.0 (C_7), 135.3 (C_1), 132.0 (C_3), 130.0 (t, $J_{C\text{-}F}$ = 11.2, C_{13}), 129.7 (C_6), 128.4 (C_5), 127.5 (C_2), 127.3 (C_4), 115.4 (t, $J_{C\text{-}F}$ = 16.4, C_{10}), 112.2 (C_{12}), 111.9 (C_{12}), 63.1 (C_{16}), 51.3 (C_{14}), 46.2, (C_8), 38.6 (C_{18}), 31.1 (C_{15}), 27.0 (C_{19}), 18.2 (C_9); **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -111.2; **IR** ν_{max}/cm^{-1} (neat): 2950, 1739 (C=O, lactam), 1645, 1622, 1460, 1426, 1265, 1229, 1210, 1138, 1090, 1032; **HRMS** (NSI): calcd. for $C_{23}H_{26}O_3NF_2^+$: 402.1875, found 402.1885, Δ 2.4 ppm; **$[\alpha]_D^{24}$** = -18.4° (*c* = 1.0, $CHCl_3$)

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a Et_2O solution of the compound.

4.8 Diastereoselectivity studies

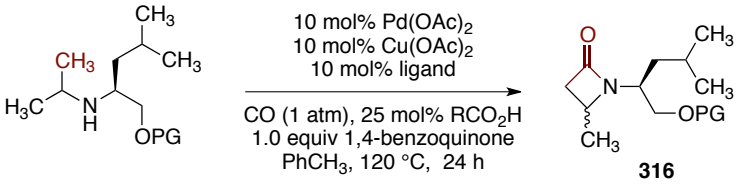
Alaninol derivatives



entry	PG	ligand	yield of **314** /%[a]	d/r of **314**[a]	yield of **315** /%[a]	ratio of **314**:**314**[a]
1	TIPS	Li-quinoline	41	1:1	12	3.4:1
2	Piv	Li-quinoline	65	1:1	28	2.3:1
3	2-pyridyl	pyridine	41	1.3:1	12	1.5:1
4	PMB	pyridine	65	1.3:1	28	1.9:1

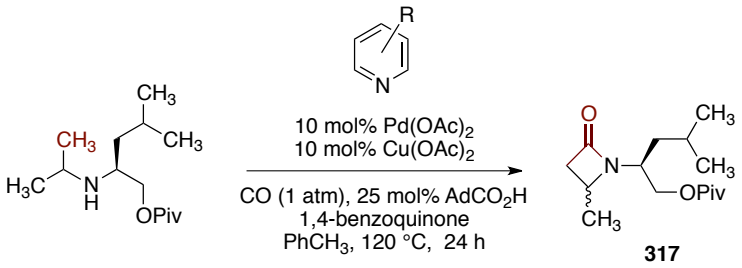
Table 16: Diastereoselectivity and regioselectivity studies on the C–H carbonylation of alaninol derivatives. [a)] Yields and ratios determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard in d^6-benzene

Isoleucinol derivatives



entry	PG	RCO_2H	ligand	yield of **316** /%[a]	d/r[a]
1	TIPS	$AdCO_2H$	Li-quinoline	25	-
2	Piv	$AdCO_2H$	Li-quinoline	42	1:1
3	Piv	$CyCO_2H$	Li-quinoline	45	1:1
4	Piv	AcOH	Li-quinoline	46	1:1
5	Piv	$AdCO_2H$	no ligand	53	1:1
6	Piv	$AdCO_2H$	2,6-lutidine	54	1:1
7	Piv	$AdCO_2H$	quinuclidine	45	1:1
8	Piv	$AdCO_2H$	pyridine	61	1:1
9	Piv	AcOH	pyridine	44	1:1
10	2-pyridyl	$AdCO_2H$	pyridine	54	1.2:1
11	2-pyridyl	$AdCO_2H$	none	18	1.2:1

Table 17: Diastereoselectivity studies on the C–H carbonylation of isoleucinol derivatives. [a)] Yields and ratios determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard in d^6-benzene

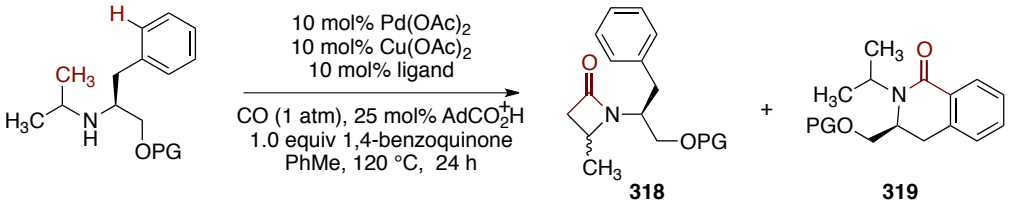


317

entry	R	ligand loading /mol%	BQ loading /equiv	yield of **317** /%[a]	d/r[a]
1	no ligand	0	1.0	53	1:1
2	H	10	1.0	61	1:1
3	H	20	1.0	57	1:1
4	H	10	2.0	55	1:1
5	4-NMe_2	10	1.0	52	1:1
6	4-OMe	10	1.0	53	1:1
7	4-CN	10	1.0	38	1:1
8	3-NO_2	10	1.0	55	1:1

Table 18: Optimisation of the pyridine ligand, with a view of observing diastereoselectivity in the C–H carbonylation of isoleucine derivatives. [a)] Yields and ratios determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard in d^6-benzene

Phenylalaninol derivatives

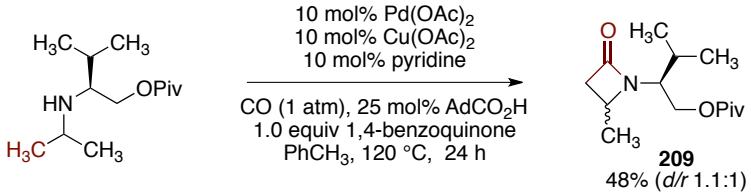


318 **319**

entry	PG	ligand	yield of **318** /%[a]	d/r of **318**[a]	yield of **319** /%[a]	ratio of **319**:**318**[a]
1	Piv	pyridine	68	1.3:1	0	-
2	2-pyridyl	pyridine	18	-[b]	45	2.5:1
3	2-pyridyl	none	10	-[b]	34	3.4:1

Table 19: Diastereoselectivity studies on the C–H carbonylation of phenylalaninol derivatives. [a)] Yields and ratios determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard in d^6-benzene; [b)] due to overlapping signals, it was not possible to determine the d/r

Valinol derivative

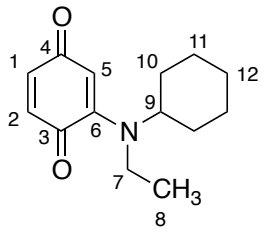


209
48% (*d/r* 1.1:1)

Scheme 76: Poorly diastereoselective C–H carbonylation of a valinol derivative, yield determined by ^{1}H NMR against a 1,1,2,2-tetrachloroethane internal standard in d^6-benzene

4.9 Isolation of the quinone side-product

2-(Cyclohexyl(ethyl)amino)cyclohexa-2,5-diene-1,4-dione **(223)**

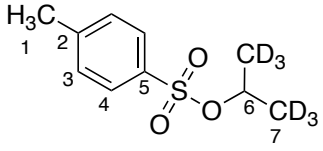


The crude material was prepared using *General Procedure H* using *N*-ethylcyclohexylamine (75 µL, 0.5 mmol). The crude material was purified by flash silica column chromatography eluting with 50% Et_2O in petroleum ether b.p. 40 – 60 °C to provide 2-(cyclohexyl(ethyl)amino)cyclohexa-2,5-diene-1,4-dione (44.3 mg, 0.19 mmol, 38%) as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.58 (1H, dd, *J* = 10.0, 2.5, H_1), 6.50 (1H, d, *J* = 10.0, H_2), 5.64 (1H, d, *J* = 2.5, H_5), 3.97 (1H, tt, *J* = 11.6, 3.1, H_9), 3.38 (2H, q, *J* = 7.0, H_7), 1.88 – 1.25 (10H, m, H_{10}, H_{11} & H_{12}), 1.18 (3H, t, *J* = 7.0, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.0 (C_4), 185.4 (C_3), 150.0 (C_6), 137.4 (C_1), 134.8 (C_2), 104.8 (C_5), 60.2 (C_9), 40.1 (C_7), 31.0 (C_{10}), 25.8 (C_{11}), 25.5 (C_{12}), 14.1 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2929, 2857, 1673 (C=O stretch), 1635 (C=O stretch), 1540 (C=C stretch), 1506, 1451, 1378, 1300, 1274, 1243, 1076, 1013; **HRMS** (APCI): calcd. for $C_{14}H_{20}O_2N^+$: 234.1489, found 234.1490, Δ 0.6 ppm

4.10 Preparation of materials for KIE studies

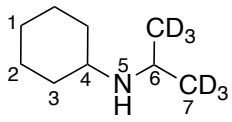
d^6-Isopropyl tosylate (**362**)



d^6-Acetone (11.0 ml, 150 mmol) was added dropwise to a stirred solution of 2.4 M $LiAlH_4$ in THF (15.6 ml, 38 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C under nitrogen for 3 h. Dry pyridine (100 ml) was added, followed by cautious and portionwise addition of tosyl chloride (57.2 g, 300 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was then poured onto ice and extracted with Et_2O (4 × 150 ml). The combined organics were washed sequentially with 3 M aq. HCl (3 × 200 ml), sat. aq. Na_2CO_3 (3 × 200 ml) and brine (200 ml). The organic was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give d^6-isopropyl tosylate (23.5 g, 107 mmol, 71%) as a clear, yellow oil.

R_f (CH_2Cl_2): 0.52**; ^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (2H, d, *J* = 8.3, H_4), 7.33 (2H, d, *J* = 8.3, H_3), 4.70 (1H, br s, H_6), 2.44 (3H, s, H_1); **^{2}H NMR** (77 MHz, $CDCl_3$) δ: 1.24 ($J_{D\text{-}H}$ = 0.9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 144.4 (C_2), 134.5 (C_5), 129.7 (C_3), 127.6 (C_4), 76.8 (C_6), 21.8 (1:3:6:7:6:3:1 septet, $J_{C\text{-}D}$ = 19.4, C_7), 21.6 (C_1); **IR** ν_{max}/cm^{-1} (neat): 1599, 1350 (S=O asymm. stretch), 1189, 1174 (S=O symm. stretch), 1136, 1099; **HRMS** (NSI): calcd. for $C_{10}H_8D_6O_3S^+$: 220.1040, found 220.1041, Δ 0.5 ppm

d^6*-N-Isopropyl cyclohexylamine* (**d^6-197**)

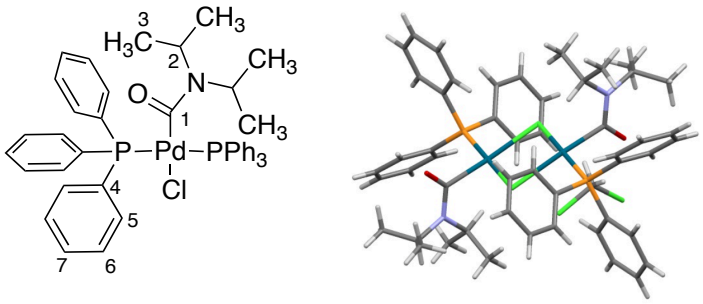


Cyclohexylamine (11.4 ml, 100 mmol) was added to a stirred suspension of d^6-isopropyl tosylate (22.0 g, 100 mmol) and potassium carbonate (15.2 g, 110 mmol) in dry acetonitrile (200 ml). The reaction mixture was heated at reflux for 24 h. The reaction mixture was filtered and 2 M HCl in Et_2O (50 ml, 100 mmol) was added to the filtrate. The solvent was then under reduced pressure to provide the HCl salt of the amine. The HCl salt was triturated with Et_2O (3 × 50 ml), then dissolved in 2 M aq. NaOH (100 ml) and then extracted with CH_2Cl_2 (4 × 100 ml). The crude material was purified by flash silica column chromatography eluting with a gradient of Et_2O to 1% aq. conc. NH_4OH and 9% CH_3OH in Et_2O. Fractions containing the product were combined, concentrated under reduced pressure to remove Et_2O. 2 M HCl in Et_2O (50 ml, 100 mmol) was added and solvent removed under reduced pressure to provide the HCl salt of the amine. The HCl salt was dissolved in 2 M aq. NaOH (100 ml) and then extracted with CH_2Cl_2 (4 × 100 ml). The resulting organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure, before finally being purified by Kugelrohr distillation (b.p. ≈ 95 °C, 95 mbar) to provide d^6-*N*-isopropyl cyclohexylamine (4.12 g, 28 mmol, 28%) as a clear, colourless oil.

R_f (1% aq. conc. NH_4OH and 9% CH_3OH in Et_2O): 0.65**; ^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.90 (1H, br s, H_6), 2.45 (1H, tt, *J* = 10.6, 3.6, H_4), 1.85 – 1.81 (2H, m, H_3), 1.70 – 1.65 (2H, m, H_2), 1.60 – 1.54 (1H, m, H_1), 1.22 (2H, br q, *J* = 12.7, H_2), 1.10 (1H, qt, *J* = 12.7, 3.5, H_1), 0.97 (2H, br q, J = 11.9, H_3), 0.67 (1H, br s, H_5); **^{2}H NMR** (77 MHz, $CDCl_3$) δ: 0.97 (d, $J_{D\text{-}H}$ = 0.8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 53.4 (C_4), 44.2 (C_6), 34.2 (C_3), 26.2 (C_1), 25.3 (C_2), 22.5 (1:3:6:7:6:3:1 septet, $J_{C\text{-}D}$ = 19.0, C_7); **IR** ν_{max}/cm^{-1} (neat): 2925, 2853, 2220 (C-D stretch), 1449, 1370, 1330, 1259, 1150, 1112, 1053; **HRMS** (NSI): calcd. for $C_9H_{14}D_6N^+$: 148.1967, found 148.1966, Δ 0.6 ppm

4.11 Preparation of palladium complexes

Bis(triphenylphosphine) palladium diisopropyl carbamoyl chloride (**293**)



$Pd(PPh_3)_4.DMSO$ was prepared according to the procedure reported in *Inorganic syntheses*.[189]

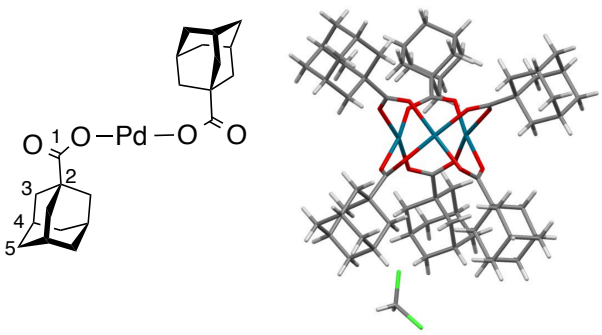
N,*N*-Diisopropylcarbamoyl chloride (1.23 g, 7.5 mmol) was added to a stirred solution of $Pd(PPh_3)_4.DMSO$ (6.17 g, 5.0 mmol) in toluene (100 ml) under nitrogen. The reaction mixture was stirred at 80 °C for 20 h. The solution was cooled to rt and concentrated under reduced pressure. The resulting residue was triturated with Et_2O (2 × 15 ml) and then toluene (2 × 15 ml). The resulting solid was dried *in vacuo* to provide Bis(triphenylphosphine) palladium diisopropyl carbamoyl chloride (3.88 g, 4.9 mmol, 98%) as a yellow powder.

m.p. 172 – 174 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.82 – 7.76 (12H, m, H_5), 7.39 – 7.31 (18H, m, H_6 & H_7), 6.27 (1H, septet, J = 6.6, H_2), 2.72 (1H, septet, J = 6.6, H_2), 0.92 (6H, d, J = 6.6, H_3), 0.30 (6H, d, J = 6.6, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.7 (t, $J_{C\text{-}P}$ = 11.3, C_1), 135.2 (t, $J_{C\text{-}P}$ = 6.3, C_5), 132.1 (t, $J_{C\text{-}P}$ = 21.3, C_4), 130.0 (C_7), 128.1 (t, $J_{C\text{-}P}$ = 5.0, C_6), 50.8 (t, $J_{C\text{-}P}$ = 3.2, C_2), 47.3 (C_2), 22.1 (C_3), 20.3 (C_3); **^{31}P** (162 MHz, $CDCl_3$) δ: 20.1; **IR** ν_{max}/cm^{-1} (neat): 1586 (C=O, Pd carbamoyl), 1481, 1433, 1249, 1094, 1029; **HRMS** (ESI): calcd. for $C_{43}H_{44}NOP_2Pd^+$: 758.1927, found 758.1929, Δ 0.2 ppm

Crystals of a chloride-bridged dimer suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the monomeric complex.

The observed characterisation data were consistent with literature values.[156]

Palladium di-1-adamantoate (**275**)



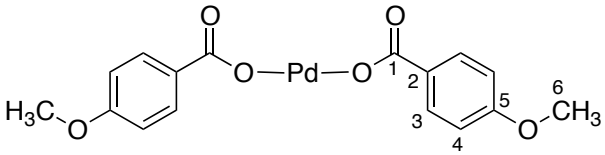
Crude complex was prepared according to *General Procedure K* using $Pd(OAc)_2$ (2.25 g, 10 mmol), 1-adamantanecarboxylic acid (5.04 g, 30 mmol) and toluene (150 ml). Acetone (30 ml) was added to the crude complex and the suspension stirred for 10 min at rt. The solid was then collected by filtration and

dried under vacuum to provide palladium di-1-adamantoate (4.66 g, 10 mmol, quant.) as a light brown powder.

m.p. 272 – 274 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.89 (6H, br s, H_4), 1.62 (24H, br s, H_3 & H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.5 (C_1), 43.0 (C_2), 39.5 (C_3), 36.6 (C_5), 28.2 (C_4); **IR** ν_{max}/cm^{-1} (neat): 2903, 2850, 1595 (C=O stretch), 1453, 1405, 1310, 115, 1090

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complex.

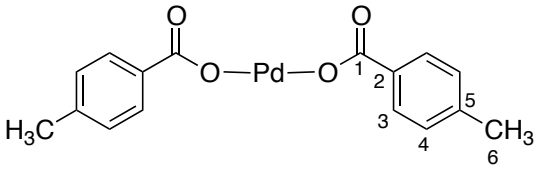
Palladium diparamethoxybenzoate **(363)**



Crude complex was prepared according to *General Procedure K* using 4-methoxybenzoic acid (915 mg, 6.0 mmol). The crude material was purified by trituration with hexane (3 × 50 ml) to provide palladium diparamethoxybenzoate (1.18 g, 2.9 mmol, 96%) as a brown solid.

m.p. 158 – 160 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08 – 7.68 (4H, m, H_3), 6.98 – 6.64 (4H, m, H_3), 3.90 – 3.70 (6H, m, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.1 (C_1), 164.0 (C_5), 162.9 (C_5), 132.4 (C_3), 131.7 (C_3), 123.9 (C_2). 121.6 (C_2), 113.8 (C_4), 112.9 (C_4), 55.5 (C_6), 55.3 (C_6); **IR** ν_{max}/cm^{-1} (neat): 1597 (C=O stretch), 1560, 1512, 1387, 1300, 1254, 1172, 1107, 1026

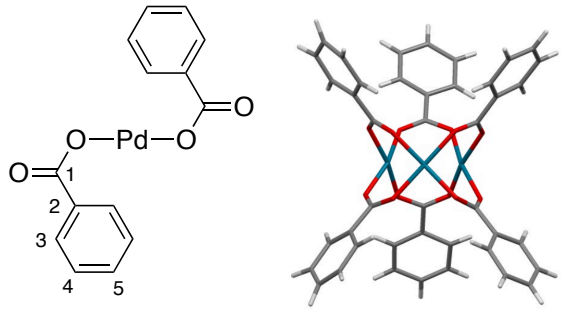
Palladium diparamethylbenzoate (**364**)



Crude complex was prepared according to *General Procedure K* using 4-methylbenzoic acid (816.9 mg, 6.0 mmol). The crude material was purified by trituration with hexane (3 × 50 ml) to provide palladium diparamethylbenzoate (1.11 g, 3.0 mmol, 99%) as a brown solid.

m.p. 148 – 150 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.01 – 7.60 (4H, m, H_3), 7.29 – 6.97 (4H, m, H_4), 2.43 – 2.26 (6H, m, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.1 (C_1), 144.6 (C_5), 130.2 (C_3), 129.2 (C_4), 128.4 (C_4), 126.4 (C_2), 21.8 (C_6); **IR** ν_{max}/cm^{-1} (neat): 1606 (C=O stretch), 1563, 1399, 1285, 1179, 1115, 1020

Palladium dibenzoate **(365)**

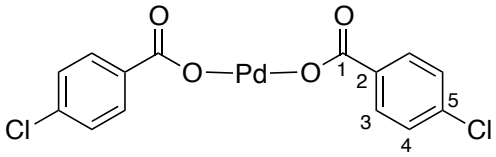


Crude complex was prepared according to *General Procedure K* using benzoic acid (732.7 mg, 6.0 mmol). The crude material was purified by trituration with hexane (3 × 50 ml) to provide palladium dibenzoate (1.02 g, 1.9 mmol, 93%) as a brown solid.

m.p. 156 – 158 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.14 – 7.74 (4H, m, H_4), 7.64 – 7.27 (6H, m, H_3 & H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.1 (C_1), 132.5 (C_5), 130.9 (C_2), 129.7 (C_4), 127.8 (C_3); **IR** ν_{max}/cm^{-1} (neat): 1685, 1607 (C=O stretch), 1571, 1400, 1325, 1291, 1179, 1128, 1072, 1026

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complex.

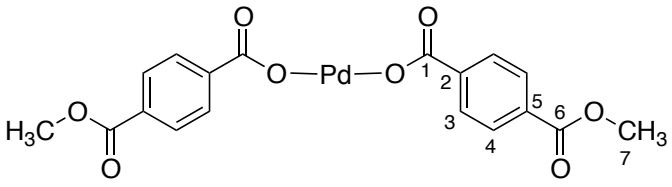
Palladium diparachlorobenzoate **(366)**



Crude complex was prepared according to *General Procedure K* using 4-chlorobenzoic acid (1.21 g, 6.0 mmol). The crude material was purified by trituration with hexane (3 × 50 ml) to provide palladium diparachlorobenzoate (537.2 mg, 1.3 mmol, 43%) as a brown solid.

m.p. 102 – 104 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.03 – 7.64 (4H, m, H_3), 7.49 – 7.18 (4H, m, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.6 (C_1), 139.2 (C_5), 131.1 (C_3), 129.3 (C_2), 128.2 (C_4); **IR** ν_{max}/cm^{-1} (neat): 1609 (C=O stretch), 1564, 1396, 1281, 1235, 1173, 1088, 1014

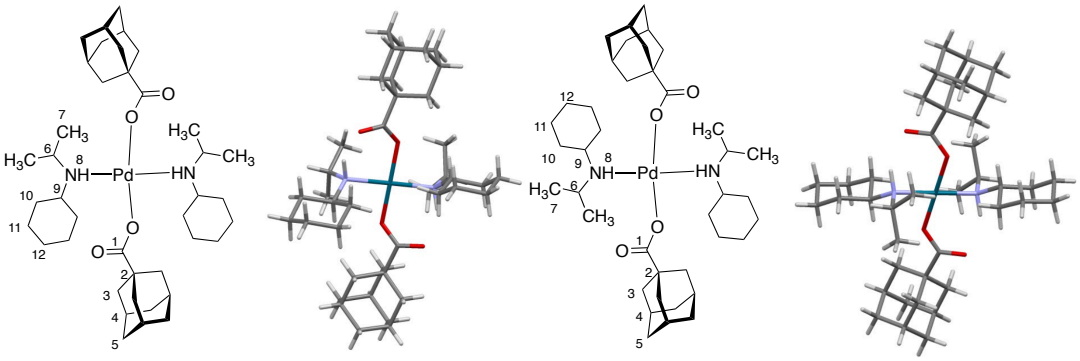
Palladium diparamethoxycarbonylbenzoate **(367)**



Crude complex was prepared according to *General Procedure K* using 4-(methoxycarbonyl)benzoic acid (1.08 g, 6.0 mmol). The crude material was purified by trituration with hexane (3 × 50 ml) to provide palladium diparamethoxycarbonylbenzoate (1.01 g, 2.2 mmol, 72%) as a brown solid.

m.p. 130 – 132 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.19 – 7.79 (8H, m, H_3 & H_4), 3.97 – 3.83 (6H, m, H_7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 181.6 (C_1), 166.2 (C_6), 134.1 (C_6), 133.7 (C_2), 130.2 (C_3), 129.7 (C_3), 129.1 (C_4), 52.4 (C_7); **IR** ν_{max}/cm^{-1} (neat): 1725, 1611 (C=O stretch), 1564, 1398, 1276, 1104, 1018

Bis(N-cyclohexylisopropylamine)palladium di-1-adamantoate (**274**)

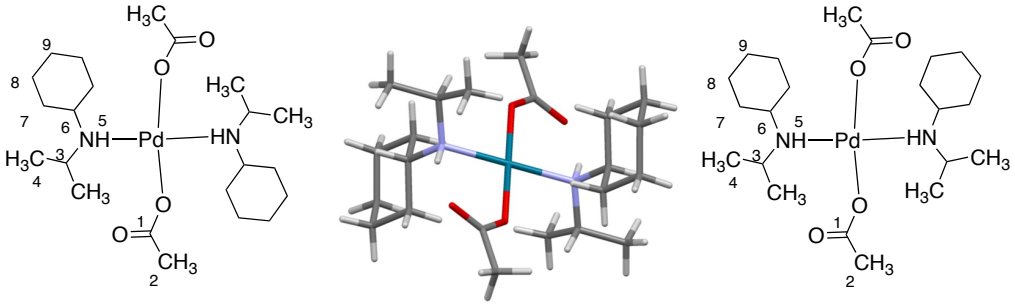


N-Cyclohexylisopropylamine (6.0 ml, 36 mmol) was added to a stirred solution of palladium(II) di-1-adamantoate (4.18 g, 9.0 mmol) in hexane (180 ml). The resulting solution was stirred at rt for 2 h. The reaction mixture was concentrated to approx. 50 ml and the resulting yellow precipitate was collected by filtration and dried under vacuum to provide palladium(II) bis(*N*-cyclohexylisopropylamine) di-1-adamantoate (5.31 g, 7.1 mmol, 79%) as a pale yellow powder.

m.p. 182 – 184 °C (decomp.); **Conformer ratio** ($CDCl_3$): 1.05: 1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.76 (2H, br s, H_8, minor conformer), 6.73 (2H, br s, H_8, major conformer), 3.19 (2H, br d, *J* = 12.3, H_{10}, major conformer), 3.11 (2H, br d, *J* = 12.4, H_{10}, minor conformer), 2.85 – 2.72 (2H, m, H_6), 2.55 – 2.41 (2H, m, H_9), 2.04 – 1.75 (6H, m, H_{10}, H_{11} & H_{12}), 1.93 (6H, br s, H_4), 1.75 – 1.72 (12H, m, H_3), 1.70 – 1.52 (8H, m, H_{10}, H_{11} & H_{12}), 1.66 – 1.64 (12H, m, H_5), 1.60 (6H, d, *J* = 6.4, H_7, major conformer), 1.55 (6H, d, *J* = 6.4, H_7, minor conformer), 1.33 (6H, d, *J* = 6.4, H_7, minor conformer), 1.30 (6H, d, *J* = 6.4, H_7, major conformer), 1.27 – 1.13 (4H, m, H_{11}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.4 (C_1), 55.4 (C_9), 47.2 (C_6, minor conformer), 47.0 (C_6, major conformer), 42.1 (C_2), 40.0 (C_3), 36.9 (C_5), 32.8 (C_{10}), 31.3 (C_{12}), 28.5 (C_4), 26.1 (C_{11}), 25.9 (C_{11}), 25.8 (C_{11}), 21.9 (C_7), 21.8 (C_7), 21.4 (C_7), 21.3 (C_7); **IR** ν_{max}/cm^{-1} (neat): 3087 (N-H stretch), 2901, 2853, 1586 (C=O stretch), 1570 (C=O stretch), 1453, 1385, 1348, 1304, 1169, 1140, 1084, 1054; **HRMS** (ESI): calcd. for $C_{40}H_{69}O_4N_2Pd^+$: 747.4287, found 747.4280, Δ 0.8 ppm

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complexes.

Bis(N-cyclohexylisopropylamine)palladium diacetate (**276**)

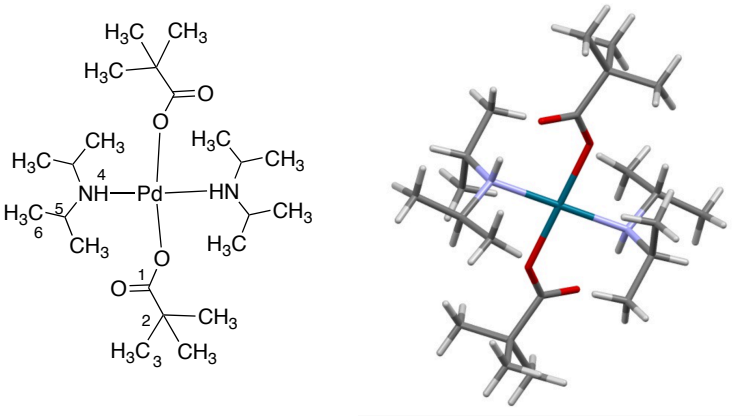


Cyclohexylisopropylamine (1.3 ml, 8.0 mmol) was added to a stirred solution of $Pd(OAc)_2$ (449 mg, 2.0 mmol) in hexane (40 ml). The resulting solution was stirred at rt for 2 h. The reaction mixture was concentrated to approx. 15 ml and the resulting yellow precipitate was collected by filtration and dried under vacuum to provide palladium(II) bis(N-cyclohexylisopropylamine) diacetate (659 mg, 1.3 mmol, 65%) as a pale yellow powder.

m.p. 134 – 136 °C (decomp.); **Conformer ratio (C_6D_6):** 2.1: 1; **^{1}H NMR** (400 MHz, C_6D_6) δ: 7.70 (2H, br s, H_5), 3.15 – 3.08 (2H, m, H_7, minor conformer), 3.04 – 2.99 (2H, m, H_7, major conformer), 2.75 (2H, septet, *J* = 6.3, H_3), 2.44 – 2.32 (2H, m, H_6), 2.25 – 2.13 (2H, m, H_7), 1.93 (6H, s, H_2), 1.87 – 1.79 (6H, m, H_8 & H_9), 1.75 (6H, d, *J* = 6.5, H_4, major conformer), 1.64 – 1.48 (4H, m, H_8), 1.32 (6H, d, *J* = 6.4, H_4, minor conformer), 1.29 (6H, d, *J* = 6.4, H_4, major conformer), 1.22 – 0.98 (6H, m, H_7 & H_9); **^{13}C NMR** (100 MHz, C_6D_6) δ: 179.9 (C_1), 56.3 (C_6, major conformer), 56.0 (C_6, minor conformer), 47.4 (C_3), 47.3 (C_3), 32.7 (C_7, minor conformer), 32.5 (C_7, minor conformer), 32.2 (C_7, major conformer), 32.0 (C_7, major conformer), 26.5 (C_8), 26.4 (C_9), 26.2 (C_9), 25.9 (C_8), 24.4 (C_2), 21.8 (C_4, minor conformer), 21.7 (C_4, major conformer), 21.6 (C_4, major conformer), 21.4 (C_4, minor conformer); **IR** ν_{max}/cm^{-1} (neat): 3093 (N-H stretch), 2928, 2855, 1586 (C=O stretch), 1453, 1370, 1319, 1224, 1176, 1158, 1137, 1106, 1080, 1062, 1013; **HRMS** (ESI): calcd. for $C_{22}H_{45}O_4N_2Pd^+$: 507.2409, found 507.2398, Δ 2.0 ppm

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complexes.

Bis(diisopropylamine)palladium dipivalate (**298**)

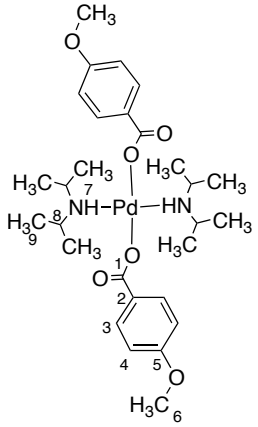


Crude complex was prepared according to *General Procedure L* using palladium pivalate (617.3 mg, 2 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(*N*-diisopropylamine) palladium dipivalate (475.8 mg, 0.93 mmol, 47%) as yellow crystals.

m.p. 128 – 130 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.84 (2H, br s, H_4), 2.76 (4H, app. octet, *J* = 6.5, H_5), 1.70 (12H, d, *J* = 6.5, H_6), 1.29 (12H, d, *J* = 6.5, H_6), 1.03 (18H, s, H_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 187.2 (C_1), 47.9 (C_5), 39.9 (C_2), 28.1 (C_3), 21.8 (C_6), 21.3 (C_6); **IR** ν_{max}/cm^{-1} (neat): 3100 (N-H stretch), 2973, 2921, 1595 (C=O stretch), 1560, 1505, 1463, 1393, 1327, 1212, 1160, 1095; **HRMS** (ESI): calcd. for $C_{22}H_{49}O_4N_2Pd^+$: 511.2722, found 511.2720, Δ 0.3 ppm

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complex.

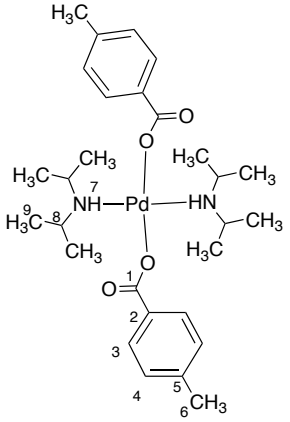
Bis(diisopropylamine) palladium diparamethoxybenzoate **(368)**



Crude complex was prepared according to *General Procedure L* using palladium diparamethoxybenzoate (817.4 mg, 2.0 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(diisopropylamine)palladium(II) diparamethoxybenzoate (1.18 g, 2.9 mmol, 96%) as an olive green powder.

m.p. 130 – 132 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.84 (4H, d, *J* = 8.2, H_3), 6.85 (4H, d, *J* = 8.2, H_4), 6.68 (2H, br s, H_7), 3.83 (6H, s, H_6), 2.87 (2H, app. octet, *J* = 6.3, H_8), 1.83 (12H, d, *J* = 6.3, H_9), 1.36 (12H, d, *J* = 6.3, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 174.7 (C_1), 161.8 (C_5), 130.9 (C_3) 127.8 (C_2), 113.0 (C_4), 55.3 (C_6), 48.4 (C_8), 21.8 (C_9), 21.6 (C_9); **IR** ν_{max}/cm^{-1} (neat): 1681, 1596 (C=O stretch), 1562, 1506, 1462, 1386, 1340, 1255, 1162, 1098, 1068, 1038; **HRMS** (ESI): calcd. for $C_{28}H_{45}O_6N_2Pd^+$: 661.2307, found 661.2312, Δ 0.84 ppm

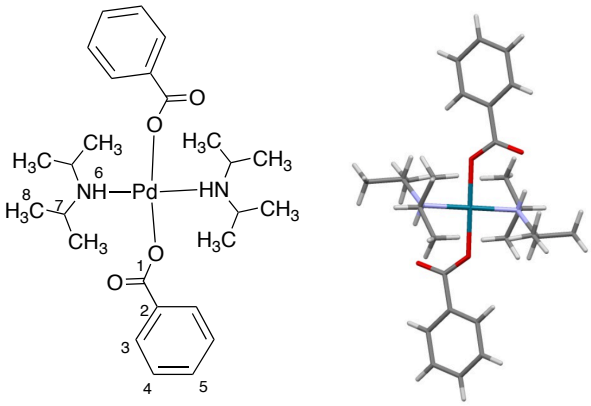
Bis(diisopropylamine) palladium diparamethylbenzoate **(369)**



Crude complex was prepared according to *General Procedure L* using palladium diparamethylbenzoate (753.4 mg, 2.0 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(diisopropylamine) palladium dibenzoate (851.9 mg, 1.5 mmol, 74%) as a brown powder.

m.p. 136 – 138 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (4H, d, *J* = 8.0, H_3), 7.16 (4H, br d, *J* = 7.3, H_4), 6.65 (2H, br s, H_7), 2.87 (4H, octet, *J* = 6.4, H_8), 2.37 (6H, s, H_6), 1.83 (12H, d, *J* = 6.4, H_9), 1.36 (12H, d, *J* = 6.4, H_9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 174.9 (C_1), 141.1 (C_5), 132.5 (C_2), 129.1 (C_3), 128.6 (C_4), 48.4 (C_8), 21.8 (C_6) 21.6 (C_9), 21.4 (C_6); **IR** ν_{max}/cm^{-1} (neat): 1601 (C=O stretch), 1565, 1403, 1342, 1291, 1171, 1095, 1069, 1015; **HRMS** (ESI): calcd. for $C_{28}H_{44}N_2O_4Pd^+$: 578.2336, found 578.2433, Δ 4.1 ppm

Bis(diisopropylamine)palladium dibenzoate (**370**)

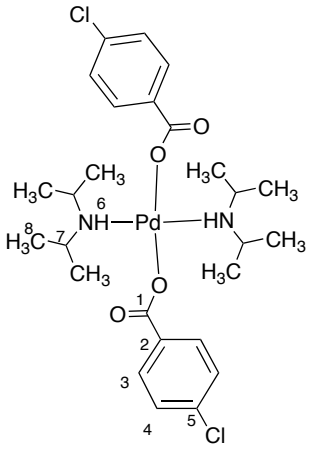


Crude complex was prepared according to *General Procedure L* using palladium dibenzoate (697.3 mg, 2.0 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(diisopropylamine) palladium dibenzoate (1.05 g, 1.9 mmol, 93%) as a brown powder.

m.p. 138 – 140 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.89 (4H, br d, *J* = 7.8, H_4), 7.45 – 7.33 (6H, m, H_3 & H_5), 2.88 (4H, septet, *J* = 6.4, H_7), 1.84 (12H, d, *J* = 6.4, H_8), 1.37 (12H, d, *J* = 6.4, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 174.8 (C_1), 135.2 (C_2), 130.9 (C_5), 129.1 (C_3), 127.8 (C_4), 48.4 (C_7), 21.8 (C_8), 21.6 (C_8); **IR** ν_{max}/cm^{-1} (neat): 1629, 1603 (C=O stretch), 1573, 1448, 1384, 1339, 1313, 1301, 1155, 1133, 1095, 1067, 1026; **HRMS** (ESI): calcd. for $C_{26}H_{41}O_4N_2Pd^+$: 551.2096, found 551.2089, Δ 1.14 ppm

Crystals suitable for x-ray crystallography were grown *via* vapour diffusion of hexane into a CH_2Cl_2 solution of the complex.

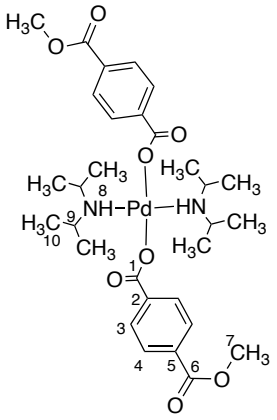
Bis(diisopropylamine) palladium diparachlorobenzoate **(371)**



Crude complex was prepared according to *General Procedure L* using palladium diparachlorobenzoate (417.5 mg, 1.0 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(diisopropylamine) palladium diparachlorobenzoate (437.9 mg, 0.71 mmol, 71%) as a brown powder.

m.p. 122 – 124 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (4H, d, *J* = 8.2, H_3), 7.32 (4H, d, *J* = 8.2, H_4), 6.49 (2H, br s, H_6), 2.84 (4H, app. octet, *J* = 6.5, H_7), 1.81 (12H, d, *J* = 6.5, H_8), 1.35 (12H, d, *J* = 6.5, H_8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.8 (C_1), 137.2 (C_5), 133.5 (C_2), 130.5 (C_3), 128.1 (C_4), 48.5 (C_7), 21.8 (C_8), 21.6 (C_8); **IR** ν_{max}/cm^{-1} (neat): 2977, 2926, 1603 (C=O stretch), 1565, 1458, 1373, 1340, 1319, 1161 1087, 1011; **HRMS** (ESI): calcd. for $C_{26}H_{38}Cl_2N_2O_4Pd^+$: 618.1258, found 618.1244, Δ 2.2 ppm

Bis(diisopropylamine)palladium diparamethoxycarbonylbenzoate (**372**)



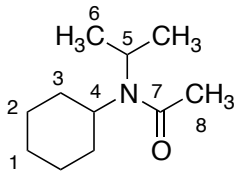
Crude complex was prepared according to *General Procedure L* using palladium diparamethoxycarbonylbenzoate (464.7 mg, 1.0 mmol). The crude complex was purified by trituration with hexane (3 × 20 ml) to provide *bis*(diisopropylamine) palladium diparamethoxycarbonylbenzoate (440.8 mg, 0.66 mmol, 66%) as a brown powder.

m.p. 148 – 150 °C (decomp.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02 (4H, d, *J* = 8.1, H_3), 7.92 (4H, d, *J* = 8.1, H_4), 6.50 (2H, br s, H_8), 3.93 (6H, s, H_7), 2.86 (4H, app. octet, *J* = 6.4, H_9), 1.83 (6H, d, *J* = 6.4, H_{10}), 1.37 (6H, d, *J* = 6.4, H_{10}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.9 (C_1), 166.7 (C_6), 139.0 (C_2), 132.1 (C_5), 129.3

(C_3), 128.9 (C_4), 52.2 (C_7), 48.5 (C_9), 21.8 (C_{10}), 21.6 (C_{10}); **IR** ν_{max}/cm^{-1} (neat): 1732 (C=O, ester), 1605 (C=O, carboxylate), 1567, 1500, 1436, 1403, 1386, 1340, 1273, 1156, 1136, 1101, 1068, 1014; **HRMS** (ESI): calcd. for $C_{30}H_{45}O_8N_2Pd^+$: 667.2205, found 667.2198, Δ 1.05 ppm

4.12 Preparation of acetylation standard

N-Cyclohexyl-N-isopropylacetamide (**277**)



Acetic anhydride (1.9 ml, 20 mmol) was added dropwise to a stirred suspension of *N*-cyclohexylisopropylamine (3.3 ml, 20 mmol) and $NaHCO_3$ (1.85 g, 22 mmol) in CH_2Cl_2 (100 ml). The reaction mixture was stirred for 16 h at rt. The reaction was filtered and the filtrate was washed with sat. aq. $NaHCO_3$ (2 × 50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product.

The crude product was purified by flash silica column chromatography eluting with 50% EtOAc in hexane to provide *N*-cyclohexyl-*N*-isopropylacetamide (3.13 g, 17 mmol, 85%) as a clear, colourless liquid.

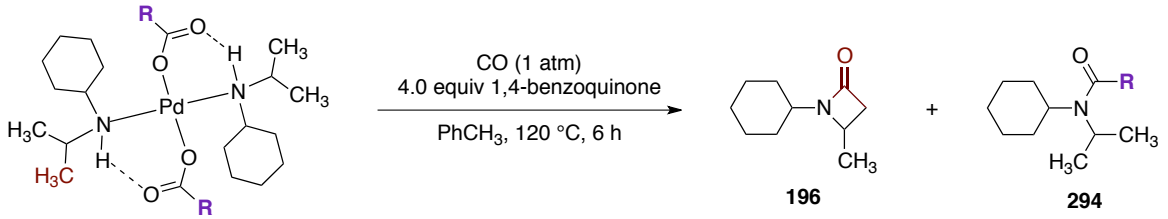
R_f (50% EtOAc/Hexane): 0.27; **Rotamer ratio**: 1.16 : 1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.89 (1H, app. septet, *J* = 6.7, H_5), 3.37 (br t, *J* = 12.8, H_4), 2.07 (3H, s, H_8, minor rotamer), 2.06 (3H, s, H_8, major rotamer), 1.83 – 1.46 (5H, m, H_1, H_2 & H_3), 1.35 (6H, d, *J* = 6.7, H_6, major rotamer), 1.31 – 1.21 (4H, m, H_2 & H_3), 1.19 (6H, d, *J* = 6.7, H_6, minor rotamer), 1.08 (1H, qt, *J* = 13.0, 3.6, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.7 (C_7, major rotamer), 169.6 (C_7, minor rotamer), 58.9 (br, C_5), 49.2 (br, C_4), 31.3 (C_3), 30.1 (C_3), 26.6 (C_2), 26.1 (C_2), 25.4 (C_1, minor rotamer), 25.3 (C_1, major rotamer), 24.1 (C_8, minor rotamer), 24.0 (C_8, major rotamer), 21.1 (C_6, minor rotamer), 20.6 (C_6, major rotamer); **IR** ν_{max}/cm^{-1} (neat): 2969, 2929, 1635 (C=O stretch), 1438, 1367, 1312, 1245, 1200, 1149, 1121, 1050; **HRMS** (NSI): calcd. for 184.1696$^+$: $C_{11}H_{22}ON$, found 184.1692, Δ 2.1 ppm

4.13 Mechanistic experiments

Effect of carboxylate sterics & electronics on the C-H carbonylation of bisamine palladium dicarboxylate complexes

Sterics

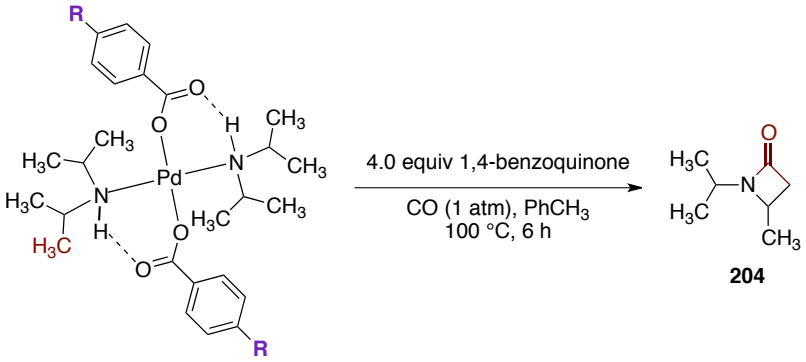
The C-H carbonylation reaction was performed according to *General Procedure M* on a range of bisamine palladium dicarboxylate complexes (0.25 mmol).



196 **294**

R	yield of **196** /%	yield of **294** /%
Me	25	5
1-Ad	89	0

Electronics

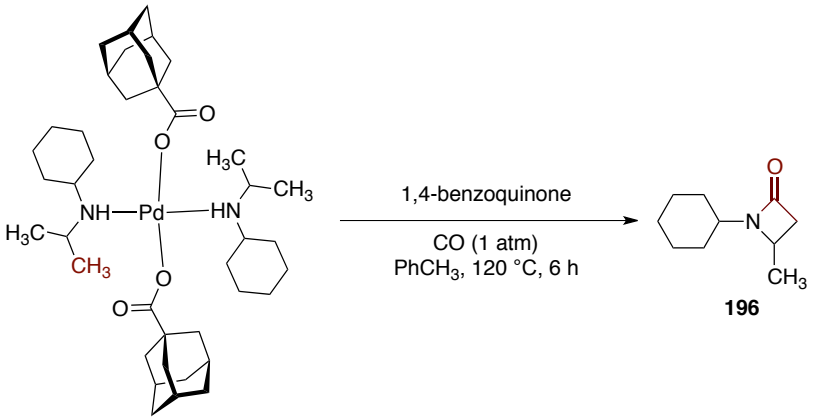


204

R	Hammett parameter σ	yield of **204** /%
OCH_3	-0.268	13
Me	-0.069	9
H	+0.000	48
Cl	+0.227	67
CO_2CH_3	+0.450	11

Effect of 1,4-benzoquinone on stoichiometric C–H carbonylation

The C-H carbonylation reaction was performed according to *General Procedure M* on bis(N-cyclohexylisopropylamine) palladium diadamantoate (186.9 mg, 0.25 mmol) with and without 1,4-benzoquinone (108 mg, 1.0 mmol).



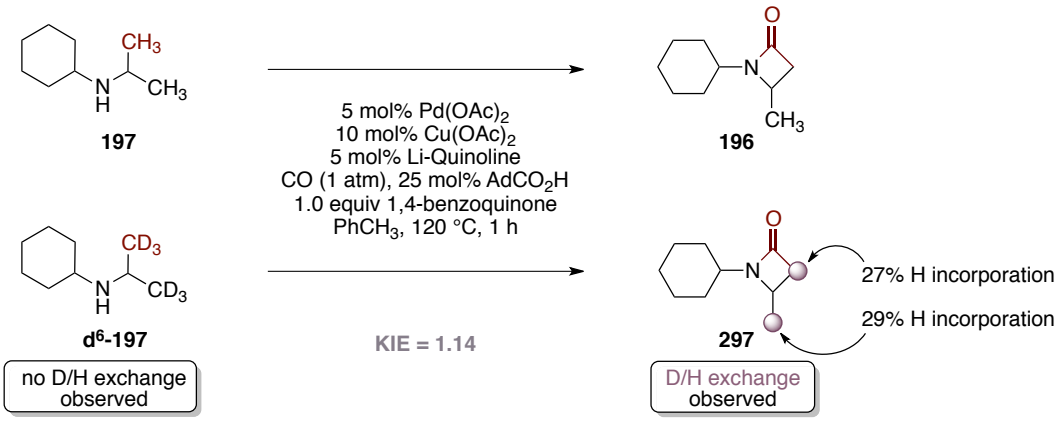
274 196

1,4-benzoquinone /equiv	yield of **196** /%
0.0	26
4.0	89

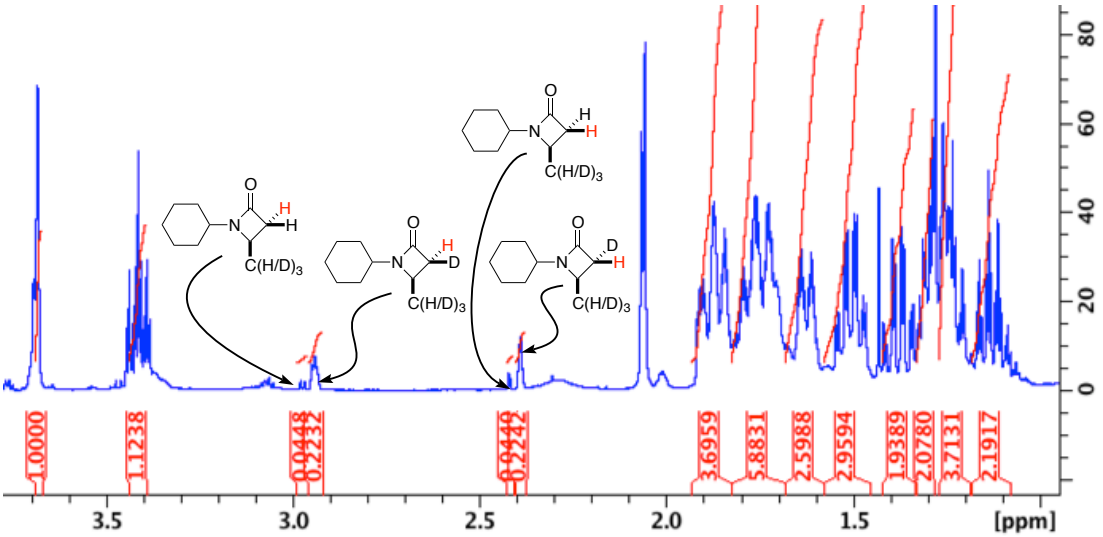
Lactam proton/deuterium scrambling experiment

The C-H carbonylation reaction was performed according to *General Procedure J* using d^6-*N*-cyclohexylisopropylamine (73.6 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol) and Li-quinoline (5.3 mg, 0.03 mmol).

The crude product was purified by flash silica column chromatography eluting with 80% Et_2O in hexane. NMR analysis indicated the lactam product had undergone proton/deuterium scrambling both alpha to the carbonyl and on the methyl of the lactam.

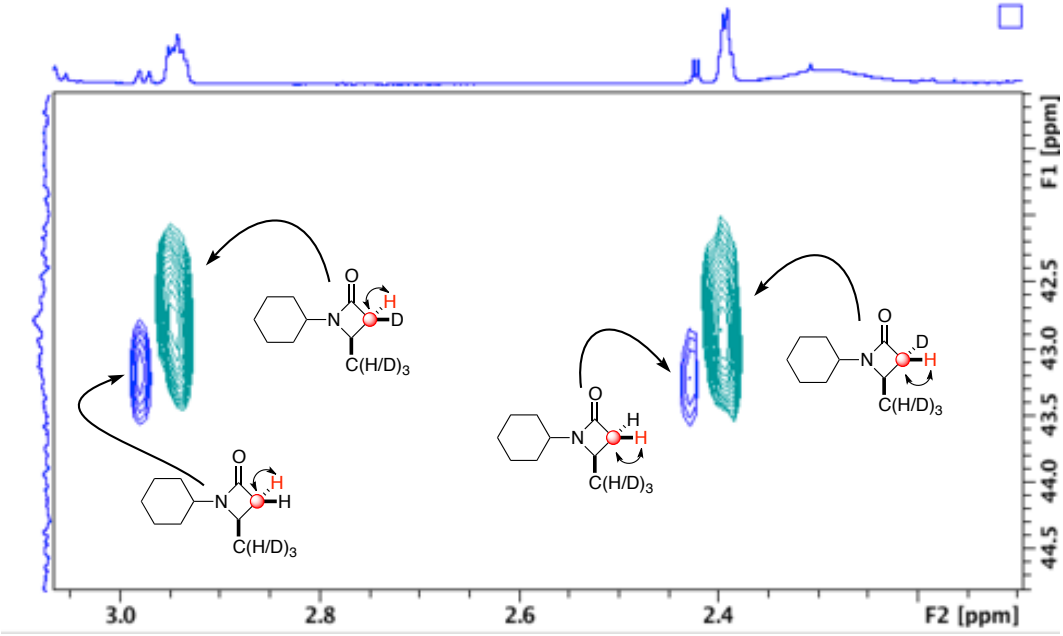


^{1}H NMR – scrambled alpha position

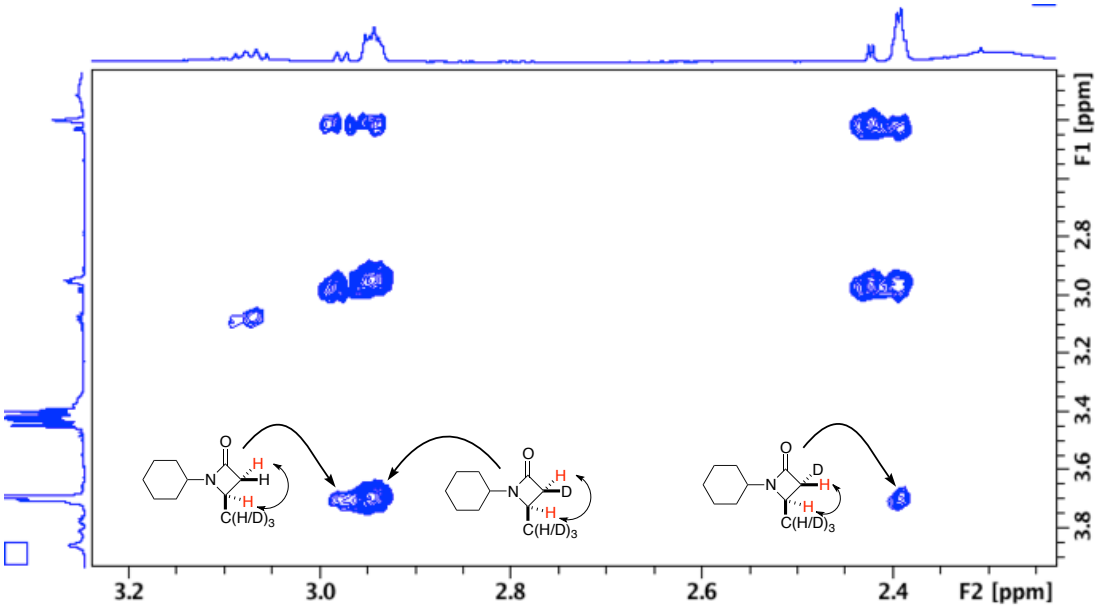


HSQC-DEPT135 – scrambled alpha position

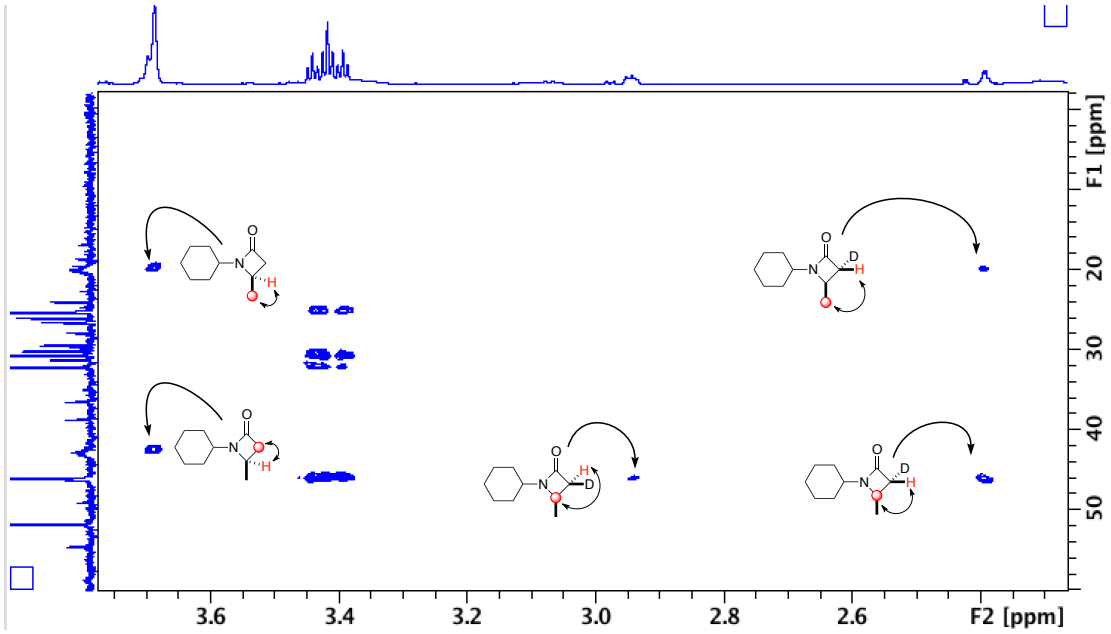
Blue indicates CH_2, green indicates CH or CH_3



COSY – scrambled alpha position

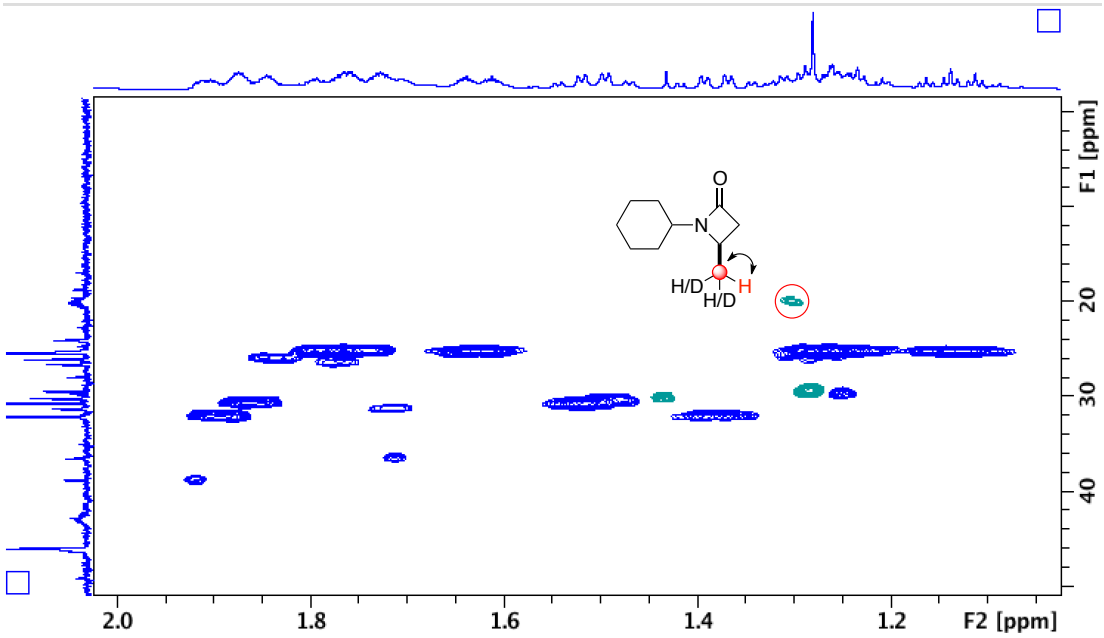


HMBC – scrambled alpha position

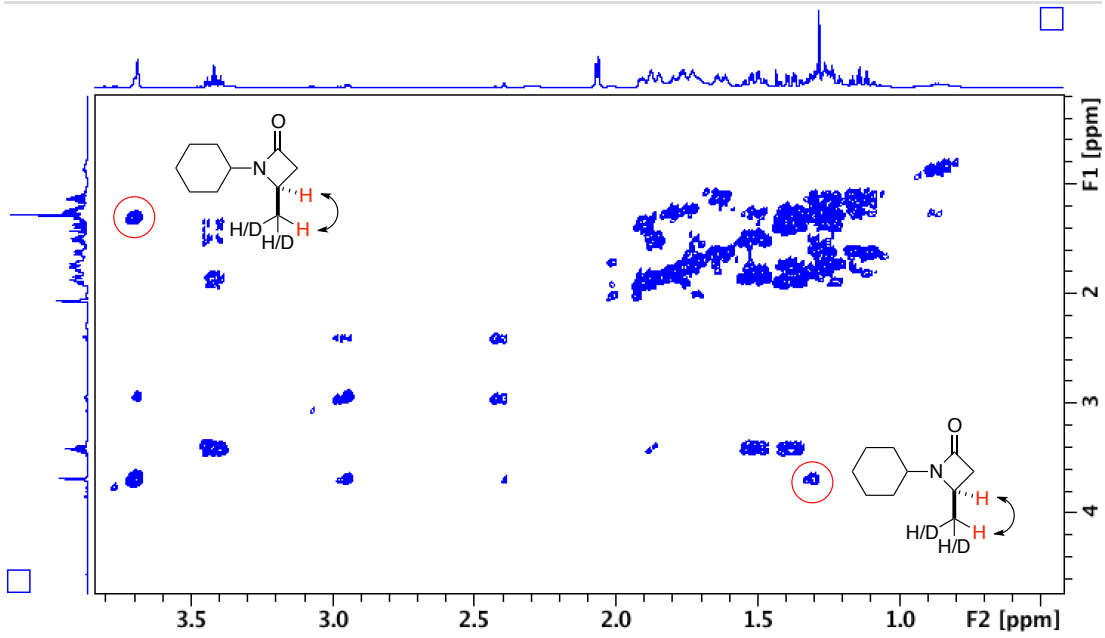


HSQC-DEPT135 – scrambled methyl

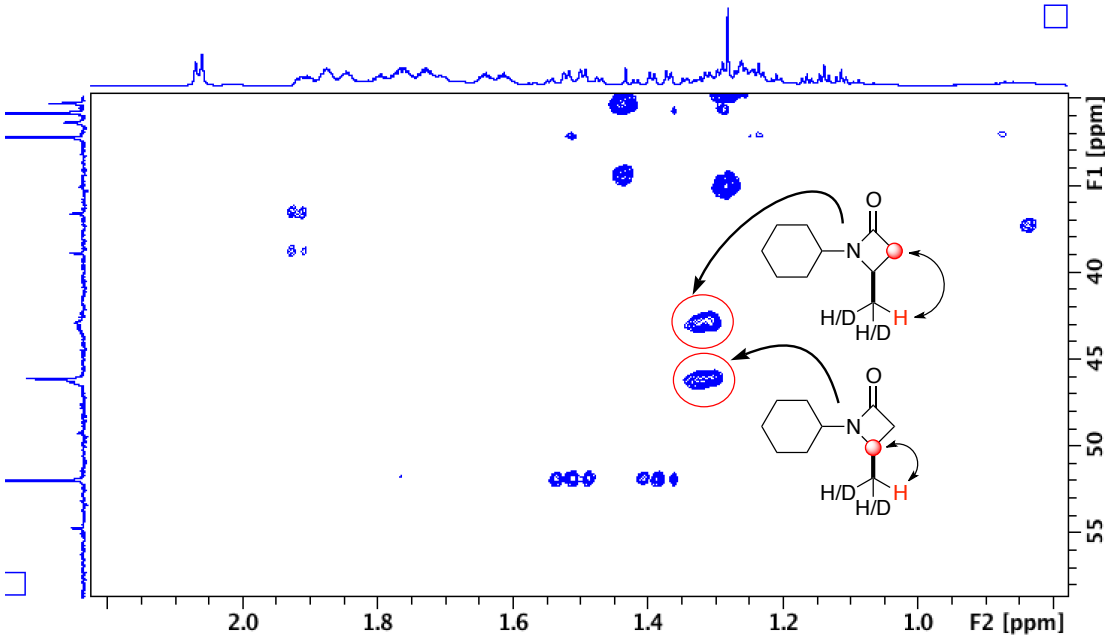
Blue indicates CH_2, green indicates CH or CH_3



COSY – scrambled methyl



HMBC – scrambled methyl



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Appendix 1: Computational experimental

A1.1 General considerations

Calculations were performed using the Amsterdam Density Functional (ADF) program[205-207] with Zero-Order Regular Approximation (ZORA) scalar relativistic BLYP-D3 exchange correlation (XC) potential, a small frozen core, 'good' numerical integration quality and solvent effects were considered using an implicit conductor like screening model (COSMO). This combination of exchange-correlation potential and basis set has been previously benchmarked for palladium catalysis by others[208,209] and also used previously within our group for studying C(sp^3)-H activation reactions of amines with palladium.[168]

Proposed intermediates were first optimised using the Universal Forcefield (UFF) molecular mechanics forcefield.[210] The resultant structures were then subjected to DFT geometry optimisation using a TZP basis set for palladium and a DZP basis set for all other atoms. Vibrational frequency analysis was then performed on structures using a TZ2P basis set for all atoms to confirm that the structures were minima. Transition states were found from DFT minimised intermediates using a series of linear transits employing a TZP basis set for palladium and a DZP basis set for all other atoms. Transition state structures were then confirmed by vibrational frequency analysis, with one negative frequency observed corresponding to the reaction co-ordinate.

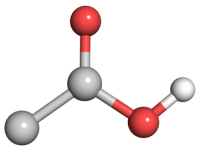
Coordinates are listed in angstroms. All enthalpies and Gibbs energies are given in kcal mol^{-1}, entropy is reported in kcal mol^{-1} K^{-1}.

The decomposition of palladium acetate under carbon monoxide was modelled at 373.15 K at 1 atm in acetic acid. All other studies were modelled at 393.15 K at 1 atm in toluene unless otherwise stated.

A1.2 Proposed mechanism for the carbon monoxide mediated decomposition of palladium acetate

A1.2A Intermediates

Acetic acid



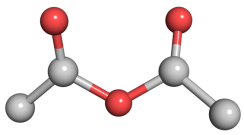
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1040.08	41.094	72.425	-1026.01

DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1028.77	41.037	73.935	-1015.32

Atom	X	Y	Z
1 C	0.377597	-1.963065	0.013591
2 C	1.775317	-1.408181	-0.020727
3 H	-0.565749	-3.622790	0.110992
4 O	-0.656379	-1.309110	-0.025318
5 H	2.303760	-1.796392	-0.901369
6 H	2.327299	-1.736668	0.869198
7 H	1.740117	-0.316143	-0.058358
8 O	0.382749	-3.333029	0.095632

Acetic Anhydride

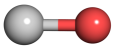


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1746.12	66.269	96.681	-1715.93

Atom	X	Y	Z
1 C	0.457396	-1.795661	-0.094441
2 C	1.785292	-1.301991	0.396085
3 C	-0.837186	-3.883959	0.109292
4 O	-0.440259	-1.136846	-0.567760
5 H	2.594350	-1.838004	-0.116251
6 H	1.873078	-1.515032	1.470056
7 H	1.868241	-0.226327	0.217669

8 O	0.405106	-3.208724	0.023026
9 C	-0.664766	-5.305801	-0.335593
10 O	-1.846611	-3.365565	0.530083
11 H	-0.360078	-5.319177	-1.390767
12 H	-1.604226	-5.850031	-0.205730
13 H	0.134774	-5.781548	0.246414

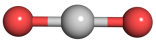
Carbon monoxide



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-333.55	4.810	48.812	-346.95

Atom	X	Y	Z
1 C	-0.969397	-2.751496	0.000000
2 O	0.168273	-2.833639	0.000000

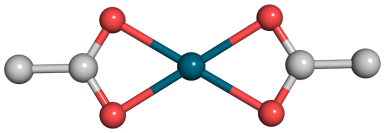
Carbon dioxide



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-514.83	9.100	53.318	-525.63

Atom	X	Y	Z
1 C	-1.118284	-2.790754	0.008100
2 O	0.055518	-2.818031	-0.001209
3 O	-2.292084	-2.763478	0.017409

Monomeric palladium diacetate **Int-1**

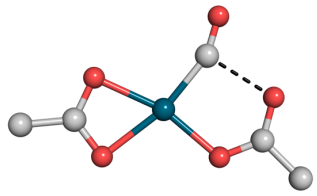


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1954.78	71.470	114.938	-1926.20

Atom	X	Y	Z
1 Pd	-0.831239	-4.727952	0.038513
2 O	-2.530601	-5.998615	0.096740
3 C	-3.316054	-4.974038	0.054965
4 O	-2.749408	-3.815282	0.006444
5 O	1.086958	-5.640539	0.071712

6 C	1.653572	-4.481789	0.022608
7 O	0.868091	-3.457205	-0.018421
8 C	-4.798148	-5.132672	0.064986
9 C	3.135642	-4.322792	0.018946
10 H	-5.104394	-5.709672	-0.817304
11 H	-5.288011	-4.153175	0.057391
12 H	-5.096508	-5.694201	0.959526
13 H	3.437272	-3.757957	-0.872384
14 H	3.625730	-5.302185	0.025030
15 H	3.438360	-3.748900	0.904507

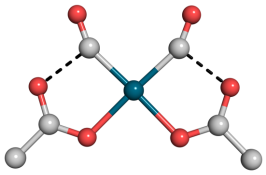
Palladium monocarbonyl diacetate **Int-2**



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2310.93	78.537	129.221	-2280.61

Atom	X	Y	Z
1 Pd	-1.584732	-3.994688	-0.021965
2 O	-3.137865	-5.464037	0.005068
3 C	-2.261528	-6.418465	0.010958
4 O	-1.016713	-6.089386	-0.024697
5 C	-2.522296	-2.291548	0.001211
6 O	-3.425793	-1.573404	0.012346
7 C	-2.688276	-7.846180	0.091511
8 O	0.253696	-3.037867	-0.038745
9 C	0.277670	-1.735892	0.009972
10 O	-0.726393	-0.982904	0.039155
11 C	1.676705	-1.141140	0.065495
12 H	-1.965487	-8.483820	-0.429865
13 H	-3.690979	-7.972764	-0.331097
14 H	-2.711925	-8.138762	1.150991
15 H	1.677166	-0.157728	-0.414910
16 H	2.405303	-1.805526	-0.408297
17 H	1.942171	-1.019001	1.124272

cis-Palladium dicarbonyl diacetate ***cis*-Int-3**



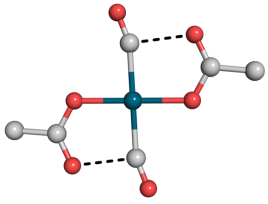
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2663.20	85.611	142.857	-2630.90

DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2619.07	85.717	148.406	-2588.73

Atom	X	Y	Z
1 Pd	-0.446512	-4.373094	-0.428814
2 O	-0.180133	-7.385669	0.153501
3 C	-1.233677	-6.945598	0.710412
4 O	-1.644307	-5.722786	0.675987
5 C	0.627338	-3.054147	-1.451815
6 O	1.526941	-2.730621	-2.103841
7 C	-2.119199	-7.922642	1.460678
8 O	-1.810103	-2.831208	0.062900
9 C	-1.538468	-1.664263	-0.416033
10 O	-0.537509	-1.381518	-1.145005
11 C	-2.500198	-0.552041	-0.040130
12 H	-2.924829	-8.231850	0.780657
13 H	-2.569029	-7.434071	2.331488
14 H	-1.547092	-8.804684	1.761639
15 H	-2.369909	0.308551	-0.702294
16 H	-2.281704	-0.251345	0.993513
17 H	-3.531421	-0.919630	-0.080429
18 C	0.783920	-5.872459	-0.855819
19 O	1.721677	-6.333260	-1.353968

trans-Palladium dicarbonyl diacetate ***trans*-Int-3**

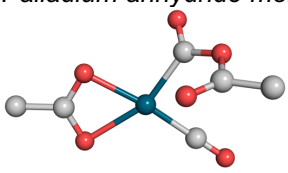


Negative, low intensity frequency at -43cm^{-1} corresponding to methyl rotation.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2658.00	84.945	146.414	-2627.69

Atom	X	Y	Z
1 Pd	0.186349	-3.488761	-0.016101
2 O	-1.844534	-3.670568	-0.325427
3 C	-2.593202	-2.602328	-0.232197
4 C	-4.078646	-2.849263	-0.460394
5 O	-2.183238	-1.450219	0.030775
6 C	0.058429	-1.523790	0.333948
7 O	0.354713	-0.445748	0.574083
8 C	0.313186	-5.448621	-0.378922
9 O	0.025182	-6.522356	-0.645748
10 O	2.214887	-3.306379	0.295871
11 C	2.965271	-4.377202	0.224916
12 C	4.440201	-4.101610	0.488089
13 O	2.558229	-5.530939	-0.027947
14 H	-4.269876	-3.869010	-0.798638
15 H	-4.448096	-2.126282	-1.194285
16 H	-4.600948	-2.669299	0.486136
17 H	4.803024	-3.361413	-0.232704
18 H	5.016938	-5.024228	0.404610
19 H	4.551641	-3.677556	1.491865

Palladium anhydride monocarbonyl **Int-4**

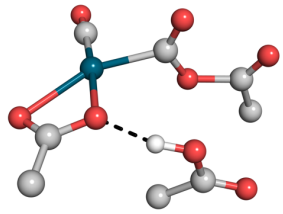


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2653.59	84.845	139.390	-2620.76

Atom	X	Y	Z
1 Pd	-0.335918	-4.881433	-0.277143
2 O	-2.098790	-6.062721	-0.652367
3 C	-1.783092	-6.937192	0.252553
4 O	-0.711860	-6.777675	0.933939
5 C	-0.636448	-3.486483	-1.755972
6 O	-0.841315	-3.855623	-2.881639
7 C	-2.680950	-8.116321	0.492247
8 O	-1.662538	-2.181254	0.514403
9 C	-0.957076	-1.568572	-0.254024
10 O	-0.526116	-2.109468	-1.494852

11 C	-0.414634	-0.182264	-0.101436
12 H	-2.077864	-9.030438	0.554594
13 H	-3.427354	-8.207832	-0.303947
14 H	-3.191554	-7.980455	1.455622
15 H	-0.685832	0.424056	-0.974475
16 H	0.682159	-0.228662	-0.057217
17 H	-0.811163	0.265255	0.813718
18 C	1.313195	-3.990372	0.215126
19 O	2.282473	-3.456785	0.516236

Palladium anhydride monocarbonyl with external acetic acid **Int-5a**



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3699.47	128.347	173.053	-3635.70

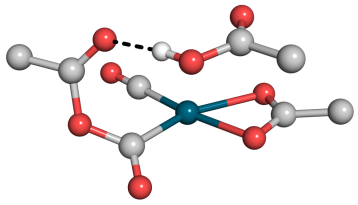
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3651.37	128.510	178.563	-3589.49

Atom	X	Y	Z
1 Pd	-0.137583	-5.194913	-0.432772
2 O	-2.154516	-5.927418	-0.690107
3 C	-1.985742	-7.067149	-0.061516
4 O	-0.832985	-7.395838	0.332637
5 C	-0.612392	-3.350430	-1.222917
6 O	-0.753712	-3.212187	-2.407613
7 C	-3.201792	-7.920112	0.164201
8 O	-1.682413	-0.752909	-1.581230
9 C	-1.385407	-1.109555	-0.483825
10 O	-0.820332	-2.486377	-0.207072
11 C	-1.481522	-0.419872	0.832475
12 H	-3.677674	-8.140628	-0.800122
13 H	-3.929064	-7.364978	0.772131
14 H	-2.931538	-8.850276	0.673332
15 H	-0.518279	-0.472381	1.353174
16 H	-2.234848	-0.934706	1.442133
17 H	-1.783291	0.618219	0.669032

18 C	1.667603	-4.599928	-0.050944
19 O	2.742535	-4.292208	0.203835
20 H	-3.303448	-4.717777	-0.645144
21 O	-3.786253	-3.831306	-0.682066
22 C	-3.828961	-3.246335	0.541650
23 O	-4.301521	-2.119905	0.656818
24 C	-3.237377	-4.028794	1.693190
25 H	-2.144007	-4.046382	1.591001
26 H	-3.589690	-5.067049	1.691738
27 H	-3.502304	-3.546248	2.639083

Palladium anhydride monocarbonyl with external acetic acid **Int-5b**



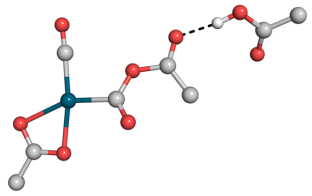
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3650.2	128.537	177.045	-3587.73

Atom	X	Y	Z
1 Pd	-0.422856	-4.821580	-0.344780
2 O	-2.033279	-6.100025	-0.962384
3 C	-1.846964	-6.915996	0.028755
4 O	-0.846247	-6.732562	0.805534
5 C	-0.624448	-3.415291	-1.825588
6 O	-1.003142	-3.744816	-2.914643
7 C	-2.837130	-8.012053	0.279571
8 O	-1.379537	-1.740522	0.317368
9 C	-0.495298	-1.386526	-0.444754
10 O	-0.204741	-2.061030	-1.630260
11 C	0.428635	-0.228238	-0.254430
12 H	-2.340629	-8.882463	0.724308
13 H	-3.352415	-8.291264	-0.645970
14 H	-3.579749	-7.633370	0.996828
15 H	0.530592	0.339173	-1.186925
16 H	1.421474	-0.624082	0.004702
17 H	0.061221	0.409499	0.553395
18 C	1.085164	-3.881376	0.428008
19 O	1.967507	-3.304634	0.877443

20 H	-2.831092	-2.739586	-0.034984
21 O	-3.649331	-3.219185	-0.359945
22 C	-3.910043	-4.247325	0.494931
23 O	-3.228404	-4.475010	1.489078
24 C	-5.084401	-5.074830	0.042205
25 H	-5.912723	-4.435647	-0.286600
26 H	-5.409312	-5.734394	0.851576
27 H	-4.760714	-5.680732	-0.814652

Palladium anhydride monocarbonyl with external acetic acid **Int-5c**



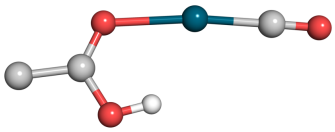
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3647.53	127.773	175.421	-3585.22

Atom	X	Y	Z
1 Pd	-0.541066	-5.765335	0.200475
2 O	-2.415301	-6.558907	-0.500869
3 C	-2.533010	-7.373839	0.502950
4 O	-1.624484	-7.398291	1.402402
5 C	-0.226451	-4.455002	-1.333328
6 O	-0.677379	-4.682613	-2.425997
7 C	-3.748946	-8.249742	0.598398
8 O	1.679049	-1.522614	-1.468232
9 C	0.730863	-2.202407	-1.800978
10 O	0.520520	-3.343735	-0.956987
11 C	-0.217932	-1.926643	-2.914614
12 H	-4.070692	-8.568360	-0.400301
13 H	-4.562781	-7.666366	1.051683
14 H	-3.543657	-9.120200	1.231170
15 H	-1.250264	-2.128952	-2.608974
16 H	0.014510	-2.594618	-3.754285
17 H	-0.094943	-0.881388	-3.214754
18 C	1.112677	-5.251161	1.073808
19 O	2.086614	-4.988876	1.617125
20 H	2.290080	-0.174854	-2.463096
21 O	2.783611	0.486679	-3.037667

22 C	1.895942	1.400362	-3.516742
23 O	0.693745	1.363276	-3.269865
24 C	2.573883	2.442307	-4.368556
25 H	3.147109	1.955809	-5.168290
26 H	3.283119	3.010785	-3.751901
27 H	1.828852	3.118731	-4.795946

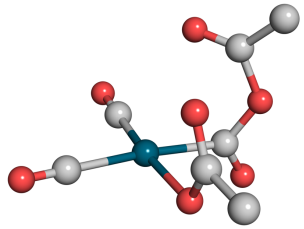
Palladium(0) carbonyl acetic acid **Int-6**



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1445.90	49.929	104.012	-1434.78

Atom	X	Y	Z
1 C	-1.688659	-3.009978	3.575271
2 O	-1.209604	-2.702516	4.589629
3 Pd	-2.480453	-3.509200	1.953460
4 O	-3.651098	-4.057671	0.151243
5 C	-4.893066	-4.015153	0.214705
6 O	-5.552490	-3.664079	1.332120
7 C	-5.786662	-4.324544	-0.943022
8 H	-6.188524	-3.376798	-1.329021
9 H	-4.857345	-3.451725	2.031914
10 H	-6.632904	-4.940352	-0.618277
11 H	-5.218946	-4.827482	-1.729732

Palladium anhydride dicarbonyl **Int-7**

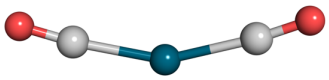


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2998.30	92.065	159.324	-2965.69

Atom	X	Y	Z
1 Pd	-0.275638	-4.532043	0.542526
2 C	-2.188013	-4.772857	0.368583
3 C	2.230465	-3.080503	0.793170

4 H	4.235213	-3.647999	1.344909
5 C	-0.222564	-3.951253	-1.451696
6 O	-0.081467	-4.742774	-2.347042
7 O	1.487138	-2.164511	1.185023
8 O	-1.690973	-1.816977	-0.229004
9 C	-0.729446	-1.589079	-0.923377
10 O	-0.132518	-2.587175	-1.741425
11 C	-0.010476	-0.288097	-1.106804
12 C	3.743400	-2.920484	0.689027
13 H	4.035319	-1.908062	0.975677
14 H	4.067444	-3.129081	-0.336715
15 H	0.179748	-0.100577	-2.168177
16 H	0.956080	-0.370651	-0.594242
17 H	-0.596220	0.520884	-0.667588
18 O	1.807265	-4.271743	0.424987
19 O	-3.318054	-4.897468	0.286672
20 C	-0.100133	-5.123192	2.501556
21 O	0.027739	-5.416045	3.590525

Palladium(0) dicarbonyl **Int-8**

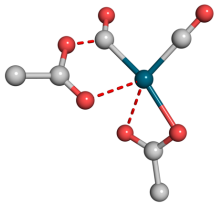


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-751.51	13.707	84.188	-769.22

Atom	X	Y	Z
1 Pd	-0.551214	-4.698625	0.822831
2 C	-2.096716	-4.806815	-0.359031
3 O	0.858353	-5.191764	3.531808
4 O	-3.064808	-4.922942	-0.966066
5 C	0.398247	-4.977774	2.501425

A1.2B Transition states

Palladium anhydride formation **TS-1**

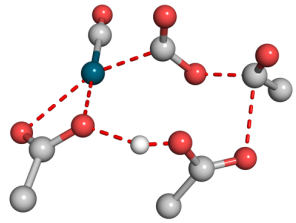


Imaginary frequency at -88 cm^{-1}

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2652.58	85.114	139.173	-2619.40

Atom	X	Y	Z
1 Pd	-0.187922	-4.713447	-0.283315
2 O	-2.263540	-5.642240	-0.531400
3 C	-2.008923	-6.407016	0.461629
4 O	-0.848801	-6.332319	1.029251
5 C	-0.056528	-3.265638	-1.673316
6 O	0.532216	-3.245838	-2.715060
7 C	-3.044614	-7.358326	0.998705
8 O	-1.693839	-2.984799	0.557328
9 C	-1.646813	-2.061564	-0.245004
10 O	-0.885283	-2.106858	-1.391653
11 C	-2.390518	-0.763380	-0.132075
12 H	-2.565591	-8.235097	1.443658
13 H	-3.734999	-7.656749	0.204874
14 H	-3.615584	-6.841843	1.781304
15 H	-3.068965	-0.662867	-0.987233
16 H	-1.680658	0.070037	-0.171929
17 H	-2.953844	-0.744080	0.801569
18 C	1.704022	-4.861994	-0.276158
19 O	2.845909	-4.959395	-0.285718

External attack - reduction of palladium anhydride monocarbonyl external acetic acid **TS-2**

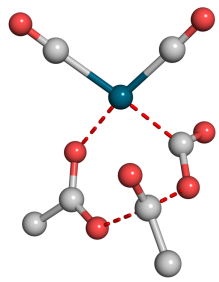


Imaginary frequency at -130 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3690.19	127.386	166.817	-3625.05

Atom	X	Y	Z
1 Pd	-0.120659	-5.193152	-0.417375
2 O	-2.154377	-5.937048	-0.711668
3 C	-2.033143	-7.087434	-0.092003
4 O	-0.907824	-7.471670	0.318834
5 C	-0.627942	-3.306941	-1.169471
6 O	-0.718705	-3.191537	-2.367066
7 C	-3.294960	-7.882129	0.125226
8 O	-2.179606	-0.937045	-1.544123
9 C	-1.758778	-1.119558	-0.458461
10 O	-0.875905	-2.515711	-0.160867
11 C	-1.464867	-0.256798	0.712314
12 H	-3.888265	-7.911822	-0.796388
13 H	-3.897624	-7.379595	0.894781
14 H	-3.060838	-8.896617	0.463086
15 H	-0.493568	0.218052	0.513111
16 H	-1.408083	-0.838408	1.633086
17 H	-2.245157	0.508070	0.777506
18 C	1.672348	-4.580434	-0.038617
19 O	2.747981	-4.260184	0.207943
20 H	-3.272035	-4.726055	-0.709183
21 O	-3.561384	-3.752089	-0.724910
22 C	-3.566913	-3.238635	0.518054
23 O	-3.506099	-2.013646	0.665988
24 C	-3.598549	-4.214229	1.666253
25 H	-2.631597	-4.735254	1.707207
26 H	-4.381605	-4.966570	1.516237
27 H	-3.760208	-3.681350	2.608135

Internal attack - reduction of palladium anhydride dicarbonyl **TS-3**



Imaginary frequency at -195 cm^{-1}, additional low intensity negative frequency at -24 cm^{-1} corresponding to bending

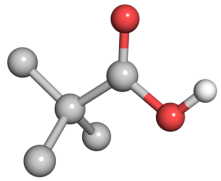
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2984.61	90.343	147.183	-2949.19

Atom	X	Y	Z
1 Pd	-0.366924	-4.547740	0.594067
2 C	-2.189539	-5.063283	0.234441
3 C	2.221851	-2.826583	0.404733
4 H	3.949596	-3.228059	1.629498
5 C	-0.278226	-3.939428	-1.419998
6 O	-0.187208	-4.796812	-2.278973
7 O	1.662056	-1.803029	-0.101959
8 O	-0.836605	-1.757295	0.539960
9 C	-0.184958	-1.543569	-0.452303
10 O	-0.255442	-2.644914	-1.661871
11 C	-0.020095	-0.242075	-1.186629
12 C	3.716078	-2.750785	0.673078
13 H	4.057733	-1.713619	0.665720
14 H	4.233622	-3.306046	-0.119068
15 H	-0.992505	0.011361	-1.623791
16 H	0.729937	-0.314268	-1.974195
17 H	0.262170	0.527071	-0.463328
18 O	1.666494	-3.949607	0.695280
19 O	-3.277477	-5.367210	0.064330
20 C	-0.264353	-5.232731	2.566011
21 O	-0.236342	-5.607742	3.637728

A1.3 Proposed mechanism for the C(sp^3)-H carbonylation of secondary amines

A1.3A Intermediates

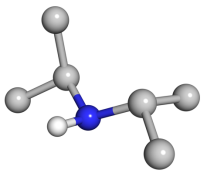
Pivalic acid



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2131.15	97.306	95.952	-2071.57

Atom	X	Y	Z
1 O	-3.430420	-1.551736	0.553561
2 C	-3.405735	-2.771512	0.505861
3 C	-4.429589	-3.665752	-0.208662
4 C	-5.501405	-2.773847	-0.869116
5 C	-5.088400	-4.607063	0.836179
6 C	-3.693451	-4.504695	-1.288803
7 O	-2.415552	-3.507038	1.113217
8 H	-5.049089	-2.094431	-1.603462
9 H	-6.023099	-2.164335	-0.119504
10 H	-6.237867	-3.407336	-1.382303
11 H	-4.343326	-5.256843	1.311850
12 H	-5.835598	-5.237678	0.334279
13 H	-5.597654	-4.026617	1.618869
14 H	-3.199284	-3.851754	-2.022094
15 H	-4.424247	-5.129816	-1.821013
16 H	-2.936851	-5.157785	-0.836169
17 H	-1.810915	-2.849620	1.543025

Diisopropylamine

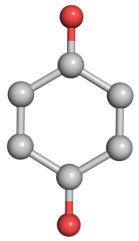


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2612.01	134.349	102.414	-2517.93

Atom	X	Y	Z
1 N	-1.100767	-3.929219	-0.708285
2 C	-2.322194	-3.421513	-0.032143

3 C	-3.337244	-3.024824	-1.118519
4 C	-2.905167	-4.493084	0.904688
5 C	0.075544	-4.235261	0.149009
6 C	1.207274	-4.742919	-0.760893
7 C	0.558948	-3.060165	1.028939
8 H	-0.806456	-3.223913	-1.397896
9 H	-2.113155	-2.516493	0.575521
10 H	-2.926383	-2.241846	-1.774675
11 H	-4.259231	-2.635022	-0.663895
12 H	-3.589813	-3.897643	-1.739058
13 H	-3.079667	-5.425333	0.345834
14 H	-3.859999	-4.149025	1.327279
15 H	-2.229819	-4.714235	1.742443
16 H	-0.219970	-5.064834	0.810931
17 H	1.544884	-3.941776	-1.438486
18 H	0.859000	-5.586805	-1.371947
19 H	2.072586	-5.067038	-0.166158
20 H	1.434401	-3.356213	1.626435
21 H	-0.222381	-2.723770	1.724205
22 H	0.847484	-2.205206	0.396826

1,4-Benzoquinone

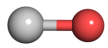


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-1778.02	57.899	87.997	-1754.72

Atom	X	Y	Z
1 C	-1.347178	-1.327573	-0.481189
2 C	-0.013331	-1.201016	-0.604351
3 C	0.892269	-2.360182	-0.398566
4 C	0.272150	-3.663475	-0.046079
5 C	-1.061701	-3.790040	0.077066
6 C	-1.967350	-2.631059	-0.129534
7 O	-3.196479	-2.747336	-0.012855
8 O	2.121419	-2.243798	-0.514892
9 H	-2.034517	-0.494030	-0.628831
10 H	0.467838	-0.256463	-0.859893

11 H	-1.542849	-4.734513	0.332940
12 H	0.959519	-4.496925	0.101958

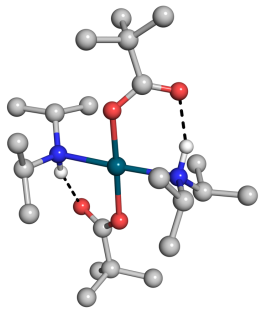
Carbon monoxide



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-333.32	4.917	49.177	-347.74

Atom	X	Y	Z
1 C	-3.819348	0.081015	0.000000
2 O	-2.678894	0.081026	0.000000

Palladium bisamine dipivalate **Int-9**



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9426.13	459.707	273.996	-9074.14

DZP:

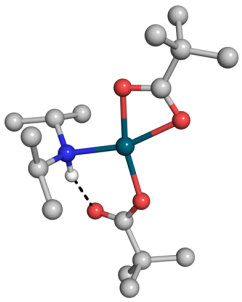
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9362.12	460.038	284.913	-9014.10

Atom	X	Y	Z
1 Pd	0.052976	0.048589	0.154448
2 O	-0.117517	2.120121	-0.078828
3 C	0.501414	2.812328	-0.990567
4 C	-0.071392	4.253171	-1.164379
5 C	-0.749247	4.756722	0.129368
6 C	-1.120868	4.156842	-2.306007
7 C	1.066650	5.214163	-1.575738
8 O	1.432945	2.413696	-1.724569
9 N	2.149054	0.026745	-0.398219
10 C	3.085764	0.219494	0.771691
11 C	3.094560	-1.003231	1.700282
12 C	2.721416	1.509281	1.524933
13 C	2.488543	-1.109683	-1.337978

14 C	3.948584	-1.041622	-1.827498
15 C	1.510471	-1.087517	-2.525411
16 H	2.138984	0.905776	-0.960494
17 H	-1.125083	5.779888	-0.021190
18 H	-0.036088	4.768109	0.966068
19 H	-1.588318	4.112929	0.416321
20 H	-1.566368	5.145633	-2.492118
21 H	-1.925831	3.458705	-2.038089
22 H	-0.650395	3.803422	-3.234124
23 H	1.818995	5.291413	-0.776633
24 H	0.659369	6.218626	-1.763746
25 H	1.568529	4.857225	-2.483156
26 H	4.097964	0.358583	0.357967
27 H	3.770233	-0.812988	2.545979
28 H	3.443916	-1.906631	1.184832
29 H	2.087287	-1.204855	2.084284
30 H	3.483044	1.709824	2.291173
31 H	1.743979	1.416344	2.016485
32 H	2.677803	2.367465	0.841943
33 H	2.330686	-2.036607	-0.776698
34 H	4.669539	-1.178556	-1.012250
35 H	4.149597	-0.076067	-2.316182
36 H	4.122951	-1.839556	-2.562701
37 H	1.552315	-0.119684	-3.045323
38 H	0.480682	-1.255671	-2.188948
39 H	1.774733	-1.881600	-3.237524
40 H	-3.082660	1.035011	-2.553420
41 O	0.239082	-2.008331	0.502458
42 C	-0.694509	-2.889769	0.289988
43 C	-0.233652	-4.342690	0.630030
44 C	1.174518	-4.605414	0.043681
45 C	-1.244090	-5.362443	0.065989
46 C	-0.183993	-4.445698	2.178351
47 O	-1.864382	-2.660905	-0.090097
48 N	-2.072016	0.057986	0.589174
49 C	-2.394780	0.280842	2.049103
50 C	-2.096491	1.722773	2.482836
51 C	-1.642812	-0.745919	2.912006
52 C	-2.861299	0.889561	-0.397857
53 C	-4.381403	0.771356	-0.171792
54 C	-2.487771	0.462754	-1.828245

55 H	-2.247808	-0.946110	0.363619
56 H	1.477653	-5.644699	0.242112
57 H	1.914158	-3.933479	0.493967
58 H	1.181873	-4.447101	-1.044865
59 H	-0.932635	-6.383268	0.333991
60 H	-1.301906	-5.291943	-1.029489
61 H	-2.248749	-5.181555	0.467833
62 H	0.508455	-3.700169	2.591733
63 H	0.154099	-5.449434	2.478581
64 H	-1.179683	-4.275350	2.612876
65 H	-3.472496	0.086482	2.176429
66 H	-2.308083	1.830959	3.555944
67 H	-2.715227	2.449963	1.942552
68 H	-1.045161	1.974341	2.296954
69 H	-1.841644	-1.769486	2.572305
70 H	-1.973541	-0.654782	3.956076
71 H	-0.558622	-0.578903	2.871299
72 H	-2.545512	1.928446	-0.250052
73 H	-4.692947	1.172477	0.800507
74 H	-4.702183	-0.279135	-0.238356
75 H	-4.908992	1.340351	-0.950295
76 H	-2.686291	-0.608376	-1.977047
77 H	-1.427002	0.650276	-2.031810

Palladium monoamine dipivalate **Int-10**



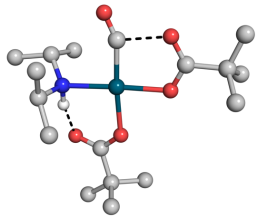
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-6781.04	321.595	219.110	-6545.59

Atom	X	Y	Z
1 Pd	-0.071247	0.198999	0.270001
2 O	0.116224	2.300119	0.118841
3 C	1.397757	2.225095	-0.065155
4 C	2.198514	3.513551	-0.256007
5 C	1.898884	4.455195	0.941247
6 C	1.716170	4.171349	-1.578692

7 C	3.708158	3.201561	-0.331938
8 O	1.943009	1.066442	-0.089112
9 H	-4.964859	1.335944	-0.927192
10 H	-2.877746	-0.675288	-1.936457
11 H	-0.900526	-4.251841	2.521643
12 H	-2.583425	1.886896	-0.250018
13 H	-3.595488	-0.026568	2.152129
14 H	0.495373	-5.338695	2.308323
15 H	-1.514316	0.466012	-2.006392
16 H	-4.797317	-0.261676	-0.158209
17 H	2.436357	5.404818	0.805821
18 H	2.230328	4.002009	1.886432
19 H	0.823772	4.663823	1.013024
20 H	2.253985	5.117560	-1.735772
21 H	0.638926	4.379160	-1.538060
22 H	1.914729	3.513081	-2.436673
23 H	4.058723	2.723258	0.592344
24 H	4.267284	4.137287	-0.475800
25 H	3.930904	2.527446	-1.169419
26 H	-0.574118	-6.290345	0.169858
27 H	0.749383	-3.575921	2.460303
28 H	1.320947	-4.223002	-1.227768
29 H	-1.174418	1.849172	2.475555
30 H	-0.704641	-0.725998	2.911963
31 H	-1.995443	-1.893502	2.544829
32 H	-2.146145	-0.820077	3.958619
33 H	-2.528681	1.683463	3.626677
34 H	-1.973719	-5.203762	0.401460
35 H	-1.088844	-5.192155	-1.138843
36 H	2.074469	-3.615196	0.265699
37 H	-4.740377	1.226859	0.827433
38 H	1.775963	-5.365044	0.062671
39 H	-2.812712	2.351780	2.005501
40 H	-3.132903	0.988879	-2.533182
41 O	0.269983	-1.843606	0.399476
42 C	-0.607134	-2.794481	0.232321
43 C	-0.021868	-4.213788	0.505768
44 C	1.377326	-4.359443	-0.137937
45 C	-0.977319	-5.290853	-0.049760
46 C	0.087825	-4.350053	2.049185
47 O	-1.817431	-2.646199	-0.051142

48 N	-2.154326	0.007990	0.615473
49 C	-2.515174	0.177020	2.075969
50 C	-2.240665	1.603916	2.569405
51 C	-1.791298	-0.883567	2.920628
52 C	-2.927850	0.850888	-0.377682
53 C	-4.448867	0.781546	-0.131119
54 C	-2.589022	0.376727	-1.801503
55 H	-2.272427	-1.002438	0.355309

cis-Palladium monoamine carbonyl dipivalate ***cis*-Int-11**

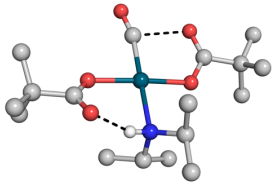


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7136.17	328.919	231.755	-6898.37

Atom	X	Y	Z
1 Pd	-0.700773	0.762836	0.555868
2 O	1.282718	1.196061	1.141355
3 C	1.755742	2.325521	0.746810
4 C	3.205556	2.630744	1.231654
5 C	4.127178	1.492034	0.725969
6 C	3.185229	2.652297	2.781891
7 C	3.686681	3.989831	0.684476
8 O	1.151889	3.174285	0.027303
9 C	-0.749543	2.430526	-0.466422
10 H	-0.754857	-3.208276	4.912974
11 H	0.935870	-3.877101	1.575189
12 H	-0.973870	-0.085573	-2.065690
13 H	-2.991038	2.876425	1.129708
14 H	-3.439420	-0.640089	2.500262
15 H	-4.299829	0.824524	3.038605
16 H	-2.091452	-2.236551	4.247643
17 H	5.156545	1.675324	1.066181
18 H	4.130516	1.451203	-0.373029
19 H	3.791425	0.521205	1.111102
20 H	4.198790	2.851144	3.158827
21 H	2.839479	1.689550	3.178424
22 H	2.519151	3.444846	3.153236

23 H	3.690846	3.994308	-0.413555
24 H	4.708875	4.183857	1.039738
25 H	3.036354	4.806276	1.024974
26 H	-2.542796	0.877158	2.748197
27 H	-1.315561	-5.140155	3.323986
28 H	-2.679840	-4.191541	2.668118
29 H	-1.452267	-4.847206	1.567381
30 H	1.335790	-2.524969	2.664733
31 H	-0.435612	-1.577808	4.248445
32 H	-4.747195	2.734481	1.368682
33 H	-2.981722	1.375552	-1.763594
34 H	-4.066870	2.662380	-0.270821
35 H	-5.247272	0.430829	-1.375720
36 H	-4.587333	-1.228676	-1.397598
37 H	-4.589727	-0.239487	-2.878193
38 H	-4.740534	0.391983	0.661124
39 H	-1.992962	-1.536476	-1.915013
40 H	-2.190890	-0.439953	-3.311175
41 O	-0.487180	-0.971045	1.734118
42 C	-1.182603	-2.067757	1.656654
43 C	-0.771012	-3.120448	2.728067
44 C	0.736435	-3.438378	2.564093
45 C	-1.608061	-4.404137	2.560121
46 C	-1.028810	-2.492557	4.123402
47 O	-2.116444	-2.299614	0.851597
48 N	-2.740700	0.248087	0.017335
49 C	-3.779858	0.851859	0.940360
50 C	-3.898338	2.370742	0.773462
51 C	-3.491350	0.450335	2.395268
52 C	-3.045179	0.320536	-1.467867
53 C	-4.457543	-0.208635	-1.788008
54 C	-1.982313	-0.484705	-2.233919
55 H	-2.655567	-0.773792	0.259161
56 H	1.052871	-4.161526	3.330902
57 O	-1.221786	3.204631	-1.190691

trans-Palladium monoamine carbonyl dipivalate ***trans*-Int-11**

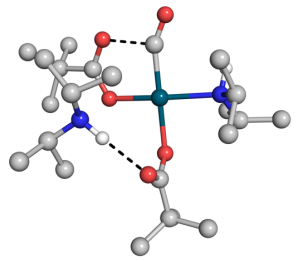


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7137.12	328.973	233.585	-6899.98

Atom	X	Y	Z
1 Pd	-0.015554	0.104214	0.060420
2 O	-0.394535	2.129037	-0.198074
3 C	0.556383	2.931807	-0.589147
4 C	0.038068	4.392110	-0.797628
5 C	-0.602435	4.882702	0.525505
6 C	-1.029393	4.357638	-1.923338
7 C	1.206442	5.314057	-1.199710
8 O	1.744859	2.622163	-0.798018
9 C	1.914839	0.256037	-0.335044
10 H	0.459740	-5.300518	2.461845
11 H	1.351954	-4.490280	-1.133101
12 H	-1.530019	0.574116	-2.159909
13 H	-1.221204	1.833912	2.265227
14 H	-1.939313	-1.926285	2.423788
15 H	-2.102197	-0.824403	3.812237
16 H	-0.911314	-4.171042	2.579104
17 H	-0.972686	5.910417	0.397784
18 H	0.135795	4.882725	1.341092
19 H	-1.439286	4.237465	0.817970
20 H	-1.416117	5.372282	-2.097372
21 H	-1.865663	3.703171	-1.648104
22 H	-0.594767	3.989097	-2.863935
23 H	1.978247	5.333580	-0.418151
24 H	0.832039	6.337029	-1.349637
25 H	1.676128	4.970958	-2.130578
26 H	-0.675308	-0.720875	2.749211
27 H	-0.635171	-6.369733	0.394892
28 H	-1.082295	-5.359514	-1.007692
29 H	-1.994819	-5.216238	0.508328
30 H	2.106072	-3.775934	0.313538
31 H	0.752547	-3.536788	2.491511
32 H	-2.566365	1.657270	3.426816
33 H	-2.766485	1.764166	-0.390290
34 H	-2.870914	2.279801	1.791375
35 H	-4.859595	0.863033	0.629680
36 H	-4.745404	-0.603381	-0.383230
37 H	-5.066987	0.982677	-1.125739

38 H	-3.591802	-0.112237	2.004463
39 H	-2.699122	-0.771558	-2.126694
40 H	-3.200119	0.843782	-2.700187
41 O	0.342683	-1.940480	0.432609
42 C	-0.525727	-2.881788	0.165094
43 C	-0.008136	-4.296325	0.577727
44 C	1.393979	-4.534353	-0.034836
45 C	-0.994119	-5.376378	0.087289
46 C	0.079484	-4.323693	2.127312
47 O	-1.665706	-2.724168	-0.317650
48 N	-2.159777	-0.072104	0.451282
49 C	-2.518613	0.116954	1.909709
50 C	-2.278709	1.560666	2.370712
51 C	-1.758011	-0.902169	2.771801
52 C	-2.999019	0.704566	-0.544721
53 C	-4.507057	0.469547	-0.331504
54 C	-2.577817	0.309584	-1.969749
55 H	-2.253052	-1.083088	0.212119
56 H	1.763511	-5.529346	0.254976
57 O	3.028303	0.027860	-0.507132

Palladium carbonyl amine dipivalate with external amine **Int-12**



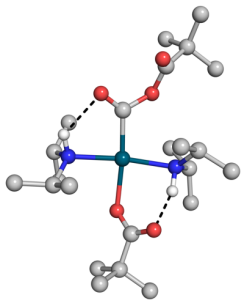
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9750.87	465.963	283.063	-9396.19

Atom	X	Y	Z
1 Pd	1.170061	0.234743	-0.674708
2 H	-1.176402	-5.160693	-0.953183
3 H	0.236400	-4.112312	-1.262818
4 H	-2.416537	2.890888	2.112152
5 H	-1.491350	4.981759	1.094353
6 H	-2.678506	4.235397	0.005205
7 H	-0.938822	4.040759	-0.326014
8 H	-1.380088	-3.587376	-1.773029
9 N	2.942913	-0.618339	0.404093
10 C	3.063936	-0.393285	1.906702

11 C	1.948526	-1.106127	2.669388
12 C	3.113837	1.107516	2.209583
13 C	3.169345	-2.056978	-0.059898
14 C	4.390210	-2.716822	0.607716
15 C	3.315186	-2.068195	-1.588739
16 H	3.709261	-0.069205	-0.015274
17 H	-0.198344	1.766680	2.593155
18 H	-0.135281	3.543648	2.737232
19 H	0.528168	2.741203	1.290510
20 H	-3.163377	2.146685	-1.027720
21 H	-4.408078	2.717133	1.065844
22 H	-4.327815	1.013376	1.583464
23 H	-5.279619	1.473362	0.144626
24 H	-3.240256	-0.726155	0.039554
25 H	-2.264860	-0.209027	-1.351603
26 H	4.035989	-0.817259	2.201768
27 H	2.085984	-0.940776	3.747242
28 H	1.954788	-2.188651	2.492027
29 H	0.964992	-0.725849	2.371072
30 H	3.336316	1.250881	3.275953
31 H	2.155065	1.585830	1.993816
32 H	3.894644	1.614186	1.625638
33 H	2.260462	-2.603052	0.208223
34 H	4.258611	-2.856075	1.687178
35 H	5.303891	-2.127054	0.435361
36 H	4.540460	-3.709897	0.162238
37 H	4.189683	-1.476953	-1.902057
38 H	2.421315	-1.667869	-2.080505
39 H	3.460478	-3.099568	-1.936800
40 H	-4.049860	-0.107870	-1.423720
41 O	0.229845	-1.652677	-0.584643
42 C	-0.583997	-1.951203	0.390473
43 C	-1.047617	-3.445417	0.385007
44 C	-2.542770	-3.511273	0.772011
45 C	-0.197216	-4.162498	1.468038
46 C	-0.825611	-4.117652	-0.986348
47 O	-0.945694	-1.193856	1.308626
48 N	-1.809099	1.622125	0.477926
49 C	-1.636494	2.815694	1.323895
50 C	-1.693263	4.097218	0.471375
51 C	-0.278400	2.710115	2.034126

52 C	-3.116635	1.430992	-0.189195
53 C	-4.355611	1.679866	0.707056
54 C	-3.170058	0.007776	-0.773678
55 H	-1.565736	0.770758	0.997289
56 H	-2.858906	-4.560724	0.870374
57 H	-3.165619	-3.035125	0.002371
58 H	-2.717987	-2.993746	1.723422
59 H	-0.507695	-5.214668	1.556231
60 H	-0.323073	-3.673444	2.443491
61 H	0.870602	-4.146134	1.204837
62 C	2.070930	1.958255	-0.900342
63 O	2.942567	2.704529	-0.703163
64 H	0.411120	1.874535	-5.208170
65 O	0.730770	2.902699	-2.097534
66 H	-2.689364	1.793085	-4.901766
67 H	-1.028736	4.605535	-2.999732
68 H	-2.413653	3.658417	-2.411105
69 H	-2.370204	4.195213	-4.108225
70 H	0.626863	3.562588	-4.668627
71 H	-0.721883	3.133730	-5.760556
72 H	-1.594621	0.501414	-4.334463
73 C	-0.115814	2.058654	-2.530532
74 O	-0.236807	0.849615	-2.134333
75 C	-1.044917	2.523221	-3.692730
76 C	-2.083496	1.442859	-4.053496
77 C	-1.756503	3.830771	-3.271611
78 C	-0.116435	2.791789	-4.909002
79 H	-2.751333	1.238859	-3.210335

Palladium anhydride bisamine pivalate **Int-13a**

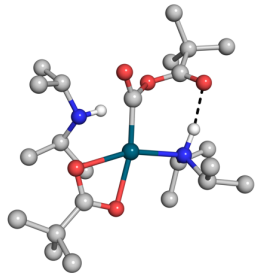


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9759.27	467.043	289.858	-9406.18

Atom	X	Y	Z
1 Pd	0.496087	-0.086359	-0.006798
2 H	1.002255	-5.667103	2.079311
3 H	0.688844	-4.035198	2.734615
4 H	-2.788138	0.999775	2.025811
5 H	-1.051783	1.439750	3.667236
6 H	-0.501746	2.062098	2.087033
7 H	0.158204	0.536982	2.718827
8 H	1.813693	-4.237407	1.382489
9 N	2.572119	-0.535848	-0.582666
10 C	3.589481	-0.334172	0.527695
11 C	3.437791	-1.387282	1.632580
12 C	3.476354	1.094540	1.081812
13 C	2.645337	-1.870802	-1.302811
14 C	4.060911	-2.183474	-1.820982
15 C	1.621829	-1.876239	-2.449707
16 H	2.752250	0.199403	-1.286121
17 H	-2.980145	-1.507824	2.231368
18 H	-2.427643	-0.756874	3.753681
19 H	-1.261416	-1.582172	2.685653
20 H	-2.519520	1.879455	-0.200975
21 H	-4.360540	0.443715	0.825644
22 H	-4.088056	-0.764680	-0.455039
23 H	-4.717297	0.852811	-0.862752
24 H	-2.067445	-0.494679	-2.098388
25 H	-2.955399	0.980527	-2.566324
26 H	4.588903	-0.434042	0.073066
27 H	4.154390	-1.169417	2.436543
28 H	3.639606	-2.401343	1.266627
29 H	2.420991	-1.379480	2.043854
30 H	4.299899	1.277835	1.785984
31 H	2.525169	1.233533	1.613964
32 H	3.531872	1.842528	0.279170
33 H	2.343020	-2.622428	-0.564815
34 H	4.788305	-2.303983	-1.008921
35 H	4.414275	-1.386309	-2.493167
36 H	4.039607	-3.123065	-2.390038
37 H	1.835894	-1.072332	-3.170126
38 H	0.601217	-1.743029	-2.070472
39 H	1.666854	-2.836582	-2.981388
40 H	-1.238038	1.084736	-2.155865

41 O	0.407317	-2.138136	0.803276
42 C	-0.516481	-2.958250	0.422413
43 C	-0.295663	-4.448410	0.820978
44 C	0.018406	-5.217388	-0.489249
45 C	-1.602976	-4.988067	1.449612
46 C	0.875018	-4.606178	1.814213
47 O	-1.540828	-2.649106	-0.240727
48 N	-1.622066	0.101414	0.498301
49 C	-1.886507	0.373328	1.975420
50 C	-0.747550	1.155634	2.648081
51 C	-2.160065	-0.952046	2.705458
52 C	-2.581013	0.811149	-0.437561
53 C	-4.023835	0.305701	-0.209051
54 C	-2.175929	0.581349	-1.902158
55 H	-1.778681	-0.913367	0.312154
56 H	0.158168	-6.288414	-0.277714
57 H	0.940244	-4.835373	-0.953258
58 H	-0.803417	-5.100807	-1.208349
59 H	-1.496178	-6.055574	1.694381
60 H	-2.441536	-4.861316	0.753523
61 H	-1.841666	-4.443984	2.376098
62 C	0.755582	1.743105	-0.780483
63 O	1.554233	2.071261	-1.632247
64 H	-2.291385	5.887531	-1.568656
65 O	-0.097131	2.761303	-0.175081
66 H	-2.545202	5.342535	1.493879
67 H	1.033848	5.686584	0.275889
68 H	0.464856	4.564997	1.536969
69 H	-0.128914	6.247452	1.504179
70 H	-0.627886	6.509133	-1.545532
71 H	-1.778894	7.006334	-0.275434
72 H	-3.072883	4.213721	0.223189
73 C	-0.588622	3.819841	-0.938512
74 O	-0.701219	3.781918	-2.145639
75 C	-1.026053	4.983188	-0.025799
76 C	-2.220509	4.513200	0.849151
77 C	0.165065	5.391160	0.880950
78 C	-1.458376	6.170306	-0.911999
79 H	-1.939757	3.668114	1.487772

Palladium anhydride monoamine pivalate with external amine **Int-14a** [Adam Smalley's work]



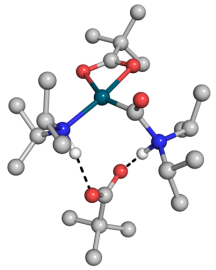
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9739.51	466.707	290.991	-9387.21

Atom	X	Y	Z
1 Pd	0.805936	-1.037641	0.611124
2 H	-1.492614	-3.660528	5.413507
3 H	-2.092608	-2.438569	4.264045
4 H	-4.099164	-1.024042	-0.385755
5 H	-4.028357	-2.541094	1.672842
6 H	-4.153028	-0.815536	2.059386
7 H	-2.582348	-1.629616	2.206569
8 H	-0.583998	-2.146736	5.154789
9 N	1.886468	-1.423272	-1.222277
10 C	3.166607	-2.162151	-0.907076
11 C	3.992184	-1.313870	0.076247
12 C	4.000633	-2.476781	-2.166284
13 C	0.894169	-2.030621	-2.212323
14 C	1.263380	-1.772268	-3.690752
15 C	0.620387	-3.512453	-1.931305
16 H	2.128607	-0.466225	-1.571123
17 H	-2.236243	-2.254193	-1.570992
18 H	-3.220814	-3.320620	-0.544580
19 H	-1.612833	-2.785472	0.009024
20 H	-1.876190	1.896045	-0.005131
21 H	-4.781291	1.083664	0.605246
22 H	-4.147839	1.571773	-0.988179
23 H	-4.170094	2.733439	0.363546
24 H	-2.330047	2.507414	2.264527
25 H	-3.138002	0.970989	2.633666
26 H	2.873902	-3.101925	-0.417539
27 H	4.922979	-1.839810	0.327307
28 H	3.439351	-1.126904	1.006189
29 H	4.249521	-0.344091	-0.374298
30 H	4.967565	-2.896348	-1.855418

31 H	4.190385	-1.560760	-2.743544
32 H	3.512699	-3.208534	-2.816278
33 H	-0.020671	-1.456797	-2.016165
34 H	2.011880	-2.479244	-4.065990
35 H	1.641885	-0.756086	-3.836455
36 H	0.354574	-1.890588	-4.297935
37 H	1.481077	-4.139337	-2.200425
38 H	0.373904	-3.689061	-0.878979
39 H	-0.233338	-3.835226	-2.542478
40 H	-1.390820	0.988265	2.321677
41 O	-0.115851	-1.350392	2.629836
42 C	0.088216	-2.607850	2.497634
43 C	-0.389236	-3.619858	3.542911
44 C	0.871790	-4.307227	4.136506
45 C	-1.272718	-4.673129	2.820926
46 C	-1.189215	-2.918222	4.661105
47 O	0.700990	-3.037268	1.442329
48 N	-2.194499	-0.125621	0.050885
49 C	-3.154179	-1.252130	0.150577
50 C	-3.502137	-1.577435	1.614428
51 C	-2.516140	-2.476370	-0.530433
52 C	-2.587166	1.238488	0.515673
53 C	-4.007841	1.677961	0.097974
54 C	-2.348339	1.433003	2.028014
55 H	-1.907971	-0.029632	-0.928293
56 H	0.565903	-5.071862	4.865097
57 H	1.508996	-3.574194	4.651386
58 H	1.460191	-4.788706	3.344765
59 H	-1.604158	-5.432821	3.543742
60 H	-0.709227	-5.167738	2.019539
61 H	-2.162140	-4.202777	2.380647
62 C	0.695844	0.879349	0.232387
63 O	0.753547	1.933800	0.729726
64 H	-1.665768	1.522865	-3.483454
65 O	-0.022997	1.140158	-1.593910
66 H	-0.294152	4.234580	-4.111002
67 H	1.736403	1.202329	-5.132291
68 H	2.427543	2.670574	-4.412721
69 H	1.152166	2.800028	-5.658429
70 H	-0.672120	0.481361	-4.530905
71 H	-1.234317	2.060493	-5.131639

72 H	0.982083	4.155116	-2.868163
73 C	0.914799	1.452129	-2.433946
74 O	2.134581	1.199108	-2.275106
75 C	0.408820	2.204582	-3.702185
76 C	0.082429	3.655091	-3.255270
77 C	1.501678	2.220074	-4.791578
78 C	-0.873122	1.522779	-4.242440
79 H	-0.681328	3.651982	-2.465823

Protonated palladium carbamoyl amine pivalate with external pivalate **Int-15** [Adam Smalley's work]



Low intensity negative frequency at -10 cm^{-1}, corresponding to pivalate rotation.

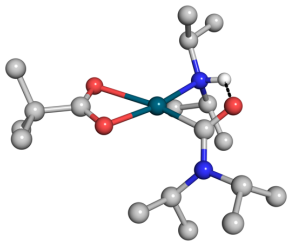
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9746.37	465.114	272.528	-9388.40

Atom	X	Y	Z
1 Pd	0.740944	-1.373910	0.619077
2 H	-1.829038	-4.938618	4.568806
3 H	-1.421926	-3.209785	4.372550
4 H	-2.443775	2.088123	1.205373
5 H	-2.411975	1.170761	3.459492
6 H	-0.803484	1.856282	3.119032
7 H	-1.056073	0.087761	3.075304
8 H	-0.131817	-4.438292	4.351142
9 N	2.018880	-0.995561	-1.098791
10 C	3.430691	-0.481629	-0.849623
11 C	3.974857	-0.905220	0.522917
12 C	3.469588	1.043179	-1.043109
13 C	1.930829	-2.194567	-2.035166
14 C	2.415203	-1.825284	-3.454268
15 C	2.658001	-3.432012	-1.492676
16 H	1.488341	-0.242552	-1.600738
17 H	-3.131339	0.077583	-0.103924
18 H	-3.742731	0.017623	1.577046
19 H	-2.347148	-0.977081	1.097228
20 H	0.482597	2.466529	-0.775934

21 H	-2.478228	3.288249	-0.556202
22 H	-1.810763	2.227351	-1.820798
23 H	-1.255888	3.907867	-1.683864
24 H	0.032256	4.647965	0.380814
25 H	-1.068105	3.853511	1.519894
26 H	4.070028	-0.932464	-1.621307
27 H	5.037076	-0.627267	0.597542
28 H	3.892865	-1.989021	0.669359
29 H	3.427087	-0.400071	1.328877
30 H	4.504434	1.399922	-0.943411
31 H	2.863874	1.550549	-0.283053
32 H	3.092079	1.323721	-2.035281
33 H	0.851807	-2.404407	-2.089974
34 H	3.509168	-1.726268	-3.495408
35 H	1.958814	-0.886355	-3.787739
36 H	2.125678	-2.624929	-4.150617
37 H	3.743403	-3.266538	-1.446749
38 H	2.293864	-3.715879	-0.499824
39 H	2.479549	-4.276033	-2.174200
40 H	0.671456	3.456733	1.539369
41 O	-0.542111	-2.109073	2.189538
42 C	-0.451478	-3.345887	1.805213
43 C	-1.340091	-4.377690	2.517980
44 C	-0.967007	-5.805878	2.070431
45 C	-2.809687	-4.058072	2.122190
46 C	-1.168664	-4.228037	4.050685
47 O	0.311977	-3.662409	0.840388
48 N	-0.697786	1.217867	0.409659
49 C	-1.918824	1.140695	1.371392
50 C	-1.506795	1.061249	2.845851
51 C	-2.840676	-0.010800	0.949588
52 C	-0.420087	2.625925	-0.170805
53 C	-1.569417	3.023194	-1.113446
54 C	-0.177569	3.699267	0.895287
55 H	-0.913327	0.580576	-0.456183
56 H	-1.619763	-6.533799	2.573339
57 H	0.076492	-6.035994	2.325986
58 H	-1.081140	-5.919251	0.984674
59 H	-3.489167	-4.773471	2.607789
60 H	-2.946431	-4.133784	1.033709
61 H	-3.082307	-3.042148	2.436621

62 C	0.616100	0.550763	1.008142
63 O	1.357866	1.234701	1.665161
64 H	0.175694	1.203990	-5.212040
65 O	-1.250703	-0.273284	-1.726652
66 H	-1.627141	-1.372854	-5.668170
67 H	-3.185618	1.237643	-3.450057
68 H	-3.279100	-0.521242	-3.222684
69 H	-3.447029	0.183461	-4.860090
70 H	-1.123645	2.260927	-4.625479
71 H	-1.417407	1.197714	-6.027409
72 H	-1.356184	-2.041320	-4.033939
73 C	-0.647443	0.229384	-2.740740
74 O	0.501691	0.766408	-2.697399
75 C	-1.394522	0.150442	-4.111066
76 C	-1.071130	-1.236989	-4.727296
77 C	-2.921881	0.267356	-3.896053
78 C	-0.907725	1.271286	-5.054459
79 H	0.000024	-1.328850	-4.946320

Palladium carbamoyl amine pivalate, **Int-16a**



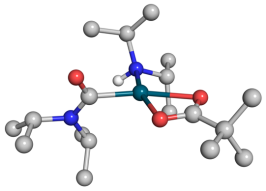
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7615.13	367.159	235.108	-7340.40

Atom	X	Y	Z
1 Pd	-0.563710	0.153029	-0.020995
2 O	0.173337	2.415262	-0.047073
3 C	1.170092	1.973923	-0.701146
4 C	2.305258	2.930878	-1.122329
5 C	2.919609	3.525239	0.173646
6 C	1.684159	4.067347	-1.974608
7 C	3.390929	2.187220	-1.929758
8 O	1.267643	0.720691	-1.013735
9 H	-5.323139	2.000846	1.032566
10 H	-4.115136	0.234867	-1.154564
11 C	-3.576898	1.145664	-0.852703
12 H	-2.788919	2.068960	0.932493

13 H	-3.358894	-0.393740	2.945144
14 C	-3.357049	1.165529	0.668484
15 H	-2.621326	1.172790	-1.391884
16 H	-5.252066	0.233612	1.234703
17 H	3.705656	4.250908	-0.082636
18 H	3.369701	2.733468	0.790541
19 H	2.147703	4.031684	0.767386
20 H	2.460275	4.797163	-2.249264
21 H	0.895540	4.581767	-1.410313
22 H	1.244804	3.666052	-2.899858
23 H	3.820060	1.363426	-1.344269
24 H	4.196645	2.885676	-2.201002
25 H	2.972908	1.760554	-2.851755
26 H	2.739899	-2.500081	2.171247
27 C	-4.707191	1.173864	1.411856
28 H	3.245618	-2.946821	-0.840941
29 H	-0.653139	1.064542	2.803695
30 H	-0.548506	-1.507596	2.457586
31 H	-2.049153	-2.416806	2.178328
32 H	-1.636210	-1.867851	3.822944
33 H	-1.525811	0.656016	4.307302
34 H	1.070683	-3.107109	2.303521
35 H	2.286624	-4.019237	1.377471
36 H	2.452318	-1.469248	-1.474086
37 H	-4.593741	1.314489	2.493672
38 H	3.522694	-1.372283	-0.066523
39 H	-2.221010	1.825319	3.165253
40 H	-4.172643	2.017803	-1.152962
41 C	-0.748930	-1.834504	-0.435938
42 N	0.330246	-2.666155	-0.302068
43 C	1.571003	-2.186555	0.380775
44 C	2.770428	-1.997230	-0.569010
45 C	1.931084	-3.012605	1.629641
46 H	-2.886050	-0.853415	0.615437
47 O	-1.863384	-2.215169	-0.833057
48 N	-2.474774	-0.010160	1.049426
49 C	-2.343520	-0.276709	2.534092
50 C	-1.647167	0.893076	3.241330
51 C	-1.598423	-1.599853	2.757707
52 C	0.095884	-4.100202	-0.705663
53 C	1.330476	-4.790700	-1.301094

54 C	-0.546556	-4.911931	0.437653
55 H	1.293978	-1.184342	0.733211
56 H	-0.650658	-4.023376	-1.506991
57 H	1.743615	-4.211619	-2.136191
58 H	1.020714	-5.773540	-1.685453
59 H	2.120999	-4.959606	-0.560923
60 H	0.159402	-5.095611	1.256142
61 H	-0.885444	-5.885267	0.052159
62 H	-1.419436	-4.377490	0.832060

Palladium carbamoyl amine pivalate **Int-16b**

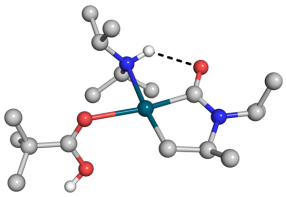


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7557.05	367.397	242.888	-7285.14

Atom	X	Y	Z
1 Pd	-0.362505	0.089835	0.556158
2 O	0.018313	2.323209	-0.124211
3 C	1.191774	1.929458	-0.425258
4 C	2.193039	2.925033	-1.050560
5 C	2.313958	4.148712	-0.106565
6 C	1.606826	3.375632	-2.415665
7 C	3.576609	2.273922	-1.256935
8 O	1.562293	0.704983	-0.235552
9 H	-5.146860	2.032743	0.216702
10 H	-3.614259	-0.101848	-1.346519
11 C	-3.108776	0.838423	-1.082480
12 H	-2.645755	2.021567	0.655211
13 H	-3.800467	-0.000916	2.845987
14 C	-3.203710	1.102376	0.428369
15 H	-2.062835	0.788111	-1.409282
16 H	-5.230730	0.331540	0.730138
17 H	2.980072	4.901889	-0.553238
18 H	2.732779	3.850743	0.865740
19 H	1.328579	4.600597	0.064307
20 H	2.268388	4.121659	-2.880352
21 H	0.611804	3.818522	-2.277547
22 H	1.515903	2.520579	-3.101869

23 H	3.998563	1.937068	-0.300521
24 H	4.266666	3.002798	-1.707952
25 H	3.505351	1.400864	-1.918893
26 H	-0.611532	-6.293119	0.697713
27 C	-4.674738	1.273643	0.855073
28 H	1.401737	-4.660736	-1.051487
29 H	-0.989122	1.200583	3.168060
30 H	-1.096942	-1.372697	3.298493
31 H	-2.548488	-2.214556	2.711084
32 H	-2.561774	-1.439887	4.311367
33 H	-2.254336	1.162964	4.426463
34 H	-1.973130	-5.150277	0.703256
35 H	-1.099731	-5.507810	-0.812506
36 H	2.103845	-3.707285	0.286309
37 H	-4.777803	1.606091	1.894694
38 H	1.816795	-5.453519	0.486507
39 H	-2.490166	2.136979	2.958097
40 H	-3.599381	1.653595	-1.631554
41 C	0.068749	-1.838471	0.988944
42 N	-0.457537	-2.858780	0.231491
43 C	0.016045	-4.241262	0.602136
44 C	1.421813	-4.529980	0.037180
45 C	-0.986806	-5.353249	0.267470
46 H	-2.871732	-0.900574	0.824346
47 O	0.834215	-2.017877	1.941744
48 N	-2.483659	-0.015269	1.178411
49 C	-2.712344	-0.030577	2.681343
50 C	-2.074365	1.196507	3.342799
51 C	-2.191459	-1.344008	3.281020
52 C	-1.187762	-2.537744	-1.027395
53 C	-0.447717	-2.989713	-2.297958
54 C	-2.668177	-2.973788	-1.023108
55 H	0.105417	-4.196390	1.696200
56 H	-1.178681	-1.438421	-1.039192
57 H	0.583392	-2.613004	-2.292846
58 H	-0.963617	-2.583061	-3.180269
59 H	-0.424740	-4.082067	-2.398259
60 H	-2.799386	-4.040020	-1.240711
61 H	-3.212607	-2.407974	-1.792205
62 H	-3.133992	-2.770438	-0.048721

Carbamoyl palladacycle amine pivalic acid **Int-17**

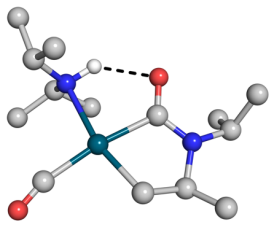


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7598.97	366.174	240.644	-7327.41

Atom	X	Y	Z
1 Pd	-0.774117	-0.889398	-0.095242
2 O	0.390964	1.222389	-0.313548
3 C	1.449040	1.543469	0.207231
4 C	2.024971	2.970632	0.151511
5 C	1.829449	3.607244	1.557347
6 C	1.242890	3.782101	-0.903928
7 C	3.531434	2.935721	-0.215433
8 O	2.136420	0.609476	0.927934
9 H	-4.183788	3.330080	0.403725
10 H	-4.067428	0.686020	-1.144282
11 C	-3.162467	1.312203	-1.113554
12 H	-1.883089	2.270353	0.321103
13 H	-3.122337	0.931783	2.996029
14 C	-2.794130	1.655436	0.339813
15 H	-2.348273	0.757153	-1.598098
16 H	-4.831132	1.829061	1.112713
17 H	2.232273	4.630028	1.549668
18 H	2.350191	3.039077	2.340712
19 H	0.764846	3.653839	1.818955
20 H	1.619760	4.813928	-0.925146
21 H	0.172129	3.801188	-0.667459
22 H	1.361837	3.342503	-1.903196
23 H	4.141214	2.445514	0.559178
24 H	3.904651	3.964122	-0.313541
25 H	3.695695	2.413457	-1.168027
26 H	1.350476	-4.310787	-2.586088
27 C	-3.928417	2.452551	1.016005
28 H	0.561308	-1.840985	-2.124137
29 H	-0.104561	0.969208	2.414612
30 H	-1.114205	-1.375211	2.752318
31 H	-2.870453	-1.578297	2.838620

32 H	-1.995679	-0.855702	4.223165
33 H	-0.881916	1.451294	3.945806
34 H	0.030596	-5.441666	-2.216528
35 H	-0.326432	-3.905645	-3.051582
36 H	-2.862211	-5.092257	-2.256436
37 H	-3.649966	2.813421	2.014796
38 H	1.556947	-2.001538	-0.645749
39 H	-1.153986	2.407871	2.475765
40 H	-3.358895	2.230976	-1.684822
41 C	-1.914851	-2.536394	-0.068141
42 N	-1.306889	-3.692743	-0.488843
43 C	0.111766	-3.626869	-0.940878
44 C	0.550726	-2.153389	-1.065985
45 C	0.297240	-4.376349	-2.277461
46 H	-3.181159	-0.303986	0.894447
47 O	-3.097625	-2.490781	0.322432
48 N	-2.425671	0.382118	1.048780
49 C	-2.221714	0.489356	2.532993
50 C	-1.018269	1.387738	2.856579
51 C	-2.041254	-0.918214	3.126143
52 C	-1.947630	-5.025131	-0.279148
53 C	-2.282014	-5.276544	1.204896
54 C	-3.161048	-5.221634	-1.207147
55 H	0.722500	-4.127264	-0.165964
56 H	-1.180713	-5.757824	-0.564645
57 H	-1.388728	-5.123160	1.827083
58 H	-2.627722	-6.312077	1.339229
59 H	-3.065995	-4.590798	1.546303
60 H	-3.937174	-4.483856	-0.970018
61 H	-3.577583	-6.232270	-1.082110
62 H	2.983999	0.995454	1.250393

Carbamoyl palladacycle amine carbon monoxide **Int-18**

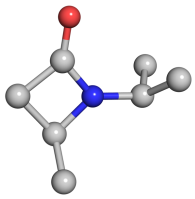


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-5819.39	273.789	195.944	-5622.64

Atom	X	Y	Z
1 Pd	-0.760128	-0.706809	-0.193482
2 C	0.623010	0.768153	-0.193258
3 O	-3.152923	-2.364030	0.129997
4 N	-2.480889	0.335408	1.055960
5 C	-2.258123	0.372162	2.543540
6 C	-1.162888	1.378806	2.921261
7 C	-1.919297	-1.043480	3.040103
8 C	-1.909998	-4.918847	-0.146844
9 H	-4.619085	3.053071	0.606011
10 H	-4.135722	0.538438	-1.114582
11 C	-3.345124	1.300803	-1.043078
12 H	-2.198124	2.333652	0.461278
13 H	-3.197136	0.678787	3.036387
14 C	-3.014178	1.596144	0.429306
15 H	-2.462709	0.923734	-1.577698
16 H	-5.050312	1.430572	1.204312
17 C	-2.226979	-4.996825	1.360782
18 C	-3.119404	-5.259684	-1.035187
19 H	0.719886	-3.781328	0.005148
20 H	-1.120978	-5.652653	-0.353175
21 H	-1.339201	-4.729361	1.951150
22 H	-2.527732	-6.021241	1.625884
23 H	-3.039880	-4.309781	1.622930
24 H	-3.927324	-4.537741	-0.867591
25 H	-3.487175	-6.269365	-0.800090
26 H	1.513997	-4.325717	-2.329865
27 C	-4.243455	2.178382	1.155855
28 H	0.182894	-1.888715	-2.344288
29 H	-0.206993	1.096908	2.459098
30 H	-0.958335	-1.380262	2.625326
31 H	-2.686621	-1.766241	2.732060
32 H	-1.849746	-1.045711	4.137226
33 H	-1.029204	1.388096	4.012236
34 H	0.350823	-5.534201	-1.750905
35 H	-0.178550	-4.273589	-2.899452
36 H	-2.833490	-5.229197	-2.095648
37 H	-4.009815	2.503237	2.177868
38 H	1.510746	-1.850192	-1.144309
39 H	-1.412387	2.400609	2.605022
40 H	-3.695156	2.213215	-1.544994

41 C	-1.953081	-2.424734	-0.201534
42 N	-1.315174	-3.593806	-0.511073
43 C	0.120451	-3.507561	-0.883186
44 C	0.442808	-2.062576	-1.287380
45 C	0.466887	-4.478127	-2.032766
46 H	-3.163674	-0.419883	0.871010
47 O	1.597158	1.389052	-0.199757

β-lactam **Int-19**

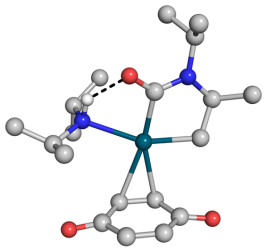


Low intensity, negative frequency at 3 cm^{-1} corresponding to isopropyl rotation.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2785.06	126.985	105.646	-2699.61

Atom	X	Y	Z
1 H	0.426196	-3.326315	-0.873601
2 H	-4.144211	-4.828491	-0.243467
3 O	-2.498825	-2.550841	-0.436180
4 C	-1.605287	-3.241656	0.048832
5 H	-4.469706	-6.304330	0.697707
6 C	-2.729256	-5.183984	1.373588
7 C	-3.467037	-4.380236	2.464352
8 C	-0.058509	-3.181582	0.097259
9 H	1.586210	-5.676873	0.531396
10 C	0.494005	-5.746437	0.455317
11 N	-1.632042	-4.390257	0.797630
12 H	0.170643	-6.620131	1.035069
13 H	0.224669	-5.908671	-0.595753
14 H	-3.131893	-6.270995	-0.477039
15 C	-0.151158	-4.469742	0.984021
16 H	0.342153	-2.290618	0.589298
17 C	-3.679154	-5.679468	0.265627
18 H	0.130973	-4.290016	2.030718
19 H	-2.243681	-6.052526	1.837924
20 H	-2.769903	-4.054056	3.244986
21 H	-4.247120	-4.994556	2.930045
22 H	-3.937304	-3.492998	2.025420

Carbamoyl palladacycle amine 1,4-benzoquinone **Int-20**

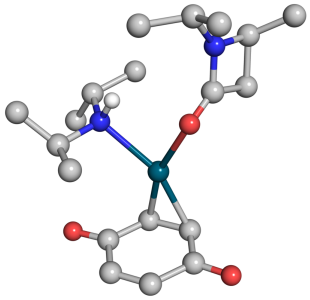


Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7255.97	327.525	223.868	-7016.46

Atom	X	Y	Z
1 Pd	-0.511181	-0.760864	0.259933
2 C	2.227240	0.221064	-0.796470
3 O	-2.976443	-2.015687	-0.554399
4 C	-1.759437	0.981934	3.329628
5 C	-2.753363	-1.309540	2.873988
6 C	-2.228213	-4.756403	-0.247145
7 C	-3.235438	-4.685172	0.916342
8 N	-2.530641	0.338386	1.031270
9 H	-4.417747	3.174436	0.296770
10 H	-3.564650	0.937153	-1.483831
11 C	-2.751617	1.567662	-1.093781
12 H	-2.071797	2.382305	0.780685
13 H	-3.787309	0.561531	2.738235
14 C	-2.843965	1.684701	0.435793
15 H	-1.801765	1.111972	-1.402658
16 H	-5.022273	1.526066	0.604294
17 C	-2.899058	-4.949673	-1.616874
18 H	0.185227	-3.961312	1.178530
19 H	-1.571604	-5.615240	-0.062663
20 H	-2.712304	-4.513025	1.867128
21 H	-3.785771	-5.634214	0.986454
22 H	-3.954948	-3.873228	0.760804
23 H	-3.550579	-4.097647	-1.846708
24 H	-3.505241	-5.866817	-1.610263
25 C	-2.777648	0.182845	2.506396
26 H	1.879571	-4.836838	-0.487356
27 C	-4.222810	2.242805	0.847615
28 H	1.041531	-2.276585	-1.240936
29 H	-0.750913	0.571165	3.184627
30 H	-1.759332	-1.739824	2.685589

31 H	-3.483879	-1.875684	2.281605
32 H	-2.995052	-1.434987	3.938980
33 H	-2.007295	0.914234	4.398471
34 H	0.417586	-5.842425	-0.452930
35 H	0.661434	-4.671622	-1.781255
36 H	-2.139844	-5.036413	-2.405967
37 H	-4.274615	2.475199	1.919071
38 H	1.718715	-2.271659	0.413989
39 H	-1.750003	2.044293	3.052157
40 H	-2.818643	2.562861	-1.552292
41 C	-1.804011	-2.308408	-0.284377
42 N	-1.309416	-3.571932	-0.253782
43 C	0.120947	-3.720324	0.101502
44 C	0.800901	-2.384251	-0.173203
45 C	0.802611	-4.844674	-0.704853
46 H	-3.129296	-0.348034	0.544883
47 C	0.725911	1.506921	0.711806
48 C	1.606689	0.462929	0.527611
49 C	0.392727	2.426565	-0.390246
50 C	0.878954	2.066607	-1.739590
51 C	1.715305	1.025699	-1.931996
52 O	3.153762	-0.594977	-0.949458
53 O	-0.254867	3.474786	-0.195814
54 H	0.393422	1.807857	1.702591
55 H	2.043628	-0.072208	1.371442
56 H	0.542011	2.703450	-2.558311
57 H	2.105580	0.765793	-2.916801

Palladium(0) amine 1,4-benzoquinone β-lactam **Int-20**



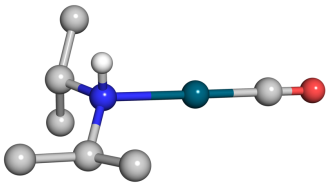
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7260.72	327.581	228.893	-7023.13

Atom	X	Y	Z
1 Pd	-0.023859	0.039175	0.352423
2 C	2.054601	0.982273	-1.478849

3 O	-0.796860	-2.104454	-0.376244
4 C	-1.964948	1.519236	3.105306
5 C	-1.660882	-1.000789	3.187010
6 C	-2.747886	-4.487654	0.397948
7 C	-3.748415	-3.316169	0.349744
8 N	-2.236804	0.113441	1.051988
9 H	-5.010503	1.926953	-0.033550
10 H	-3.266493	-0.140410	-1.496521
11 C	-2.824466	0.835295	-1.241416
12 H	-2.532260	2.111496	0.469403
13 H	-3.498207	0.031777	2.776260
14 C	-3.003689	1.142054	0.254154
15 H	-1.760724	0.811226	-1.512619
16 H	-4.973962	0.220264	0.473400
17 C	-2.622511	-5.202452	-0.961714
18 H	-0.824918	-4.504542	2.863554
19 H	-3.079097	-5.209309	1.161510
20 H	-3.813129	-2.815696	1.325251
21 H	-4.747532	-3.687889	0.084377
22 H	-3.435947	-2.585813	-0.407870
23 H	-2.245453	-4.500018	-1.718603
24 H	-3.602387	-5.578624	-1.287576
25 C	-2.426559	0.167233	2.545661
26 H	0.803247	-6.314392	2.221870
27 C	-4.500728	1.204308	0.618978
28 H	1.426956	-3.748227	0.901511
29 H	-0.935954	1.730868	2.788443
30 H	-0.578967	-0.867463	3.045157
31 H	-1.950718	-1.963764	2.744112
32 H	-1.872963	-1.042571	4.264838
33 H	-2.005914	1.499287	4.203322
34 H	-0.830153	-6.730778	1.650310
35 H	0.378597	-6.095467	0.500011
36 H	-1.926942	-6.048850	-0.892850
37 H	-4.667179	1.519581	1.656387
38 H	0.741068	-2.694984	2.189079
39 H	-2.593914	2.347907	2.757131
40 H	-3.321241	1.606098	-1.846298
41 C	-0.615416	-3.010790	0.452778
42 N	-1.426627	-4.023555	0.855374
43 C	-0.448907	-4.599227	1.833402

44 C	0.509519	-3.430997	1.412342
45 C	0.000951	-6.021620	1.529482
46 H	-2.568673	-0.808430	0.738957
47 C	1.168902	1.776695	0.740045
48 C	1.989218	0.886779	-0.015069
49 C	0.320680	2.778576	0.069022
50 C	0.388283	2.830357	-1.420060
51 C	1.188765	2.011669	-2.129360
52 O	2.801311	0.263262	-2.178763
53 O	-0.423731	3.565684	0.695364
54 H	1.347514	1.939628	1.805521
55 H	2.796779	0.328011	0.462670
56 H	-0.242798	3.583348	-1.895527
57 H	1.250961	2.060133	-3.218110

Amine palladium(0) carbon monoxide



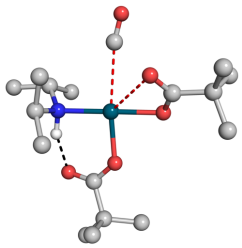
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-3029.18	144.729	135.105	-2937.57

Atom	X	Y	Z
1 Pd	0.237701	0.591986	0.554645
2 H	-2.038288	-0.747499	0.245049
3 H	-4.727419	1.088339	0.535719
4 C	-2.452998	1.549601	2.676182
5 C	-1.830831	-0.913928	2.813992
6 C	-4.246565	0.811309	-0.407646
7 C	2.062978	0.887716	0.506500
8 N	-1.969314	0.214390	0.599828
9 H	-4.715657	1.403032	-1.202171
10 H	-2.286444	-0.187455	-2.124488
11 C	-2.129859	0.849355	-1.796649
12 H	-2.546694	2.113901	-0.103908
13 H	-3.607404	-0.109067	1.928498
14 C	-2.729125	1.075424	-0.399915
15 H	-1.051703	1.052205	-1.802489
16 H	-4.456638	-0.248258	-0.606965

17 H	-1.406815	1.876397	2.731864
18 H	-0.771864	-0.663854	2.955968
19 H	-1.888760	-1.888893	2.313680
20 H	-2.301603	-1.011728	3.799020
21 H	-2.853315	1.488952	3.694721
22 H	-3.024511	2.313129	2.137601
23 H	-2.612355	1.511035	-2.524637
24 O	3.208966	1.075547	0.461215
25 C	-2.548922	0.174557	2.002606

A1.3B Transition states

Carbon monoxide binding to palladium monoamine dipivalate **TS-4**



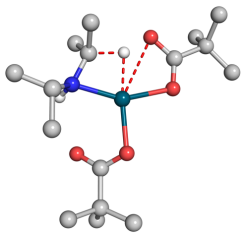
Imaginary frequency at -153 cm^{-1}

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7106.51	327.575	237.440	-6872.28

Atom	X	Y	Z
1 Pd	-0.651543	0.615748	0.432033
2 O	1.351911	0.978073	0.872641
3 C	1.511288	2.246148	1.149739
4 C	2.966836	2.645004	1.502094
5 C	3.844572	2.390340	0.246679
6 C	3.459434	1.763894	2.678026
7 C	3.021992	4.137172	1.890238
8 O	0.576838	3.081052	1.111786
9 C	-0.534268	2.672527	-1.385624
10 H	-1.181892	-3.120663	5.002755
11 H	1.129594	-3.577797	2.021081
12 H	-1.018029	-0.427105	-2.066416
13 H	-2.484074	2.903511	0.900970
14 H	-3.482259	-0.405294	2.506599
15 H	-4.131904	1.184614	2.981942
16 H	-2.512374	-2.369330	4.085156
17 H	4.887774	2.670556	0.456289
18 H	3.492175	2.991964	-0.604175

19 H	3.813463	1.330977	-0.039112
20 H	4.500240	2.020516	2.927008
21 H	3.407828	0.700205	2.413611
22 H	2.840643	1.927653	3.572762
23 H	2.671017	4.770981	1.065155
24 H	4.057701	4.416997	2.134374
25 H	2.388172	4.340062	2.764209
26 H	-2.387222	0.986610	2.679819
27 H	-1.206533	-5.137167	3.397224
28 H	-2.557495	-4.380791	2.505011
29 H	-1.088843	-4.878245	1.635746
30 H	1.160068	-2.219123	3.167866
31 H	-0.991531	-1.470732	4.342484
32 H	-4.219404	3.099463	1.241525
33 H	-2.832400	1.282186	-1.850514
34 H	-3.676316	2.814423	-0.423944
35 H	-5.192535	0.642846	-1.398396
36 H	-4.738534	-1.083840	-1.347913
37 H	-4.636949	-0.169512	-2.873148
38 H	-4.664943	0.743847	0.633059
39 H	-2.202543	-1.731375	-1.831162
40 H	-2.278990	-0.704879	-3.291521
41 O	-0.455230	-1.035039	1.675215
42 C	-1.235428	-2.080773	1.698598
43 C	-0.835595	-3.069536	2.846266
44 C	0.701118	-3.192232	2.957702
45 C	-1.465152	-4.451828	2.576407
46 C	-1.418935	-2.464081	4.152101
47 O	-2.228341	-2.302602	0.977804
48 N	-2.715309	0.238900	-0.010888
49 C	-3.635433	1.047607	0.879891
50 C	-3.489907	2.554577	0.626647
51 C	-3.388567	0.677371	2.351914
52 C	-3.022127	0.260151	-1.495038
53 C	-4.490794	-0.105714	-1.786122
54 C	-2.068624	-0.709988	-2.213459
55 H	-2.762963	-0.761329	0.293899
56 H	0.957767	-3.891196	3.767654
57 O	-0.299261	3.645081	-1.930439

β-hydride elimination of palladium monoamine dipivalate **TS-5**



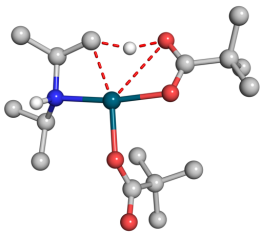
Imaginary frequency at -1033 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-6753.25	317.422	219.095	-6521.97

Atom	X	Y	Z
1 Pd	-0.307378	0.163133	0.475216
2 O	-0.184334	2.753011	-0.829432
3 C	1.047825	2.364131	-0.787586
4 C	2.086239	3.319704	-1.422888
5 C	3.519741	2.786485	-1.223242
6 C	1.938841	4.714372	-0.760990
7 C	1.759833	3.416383	-2.938200
8 O	1.447473	1.266320	-0.283973
9 H	-2.412223	3.359632	0.446408
10 H	-3.960643	1.204216	-1.180461
11 H	1.610703	-4.502829	-0.766715
12 H	-0.958201	1.795692	-0.247988
13 H	-2.712402	0.557203	2.770127
14 H	1.227464	-5.945941	0.207532
15 H	-2.530339	0.351113	-1.837081
16 H	-3.754848	2.436113	1.163128
17 H	4.236253	3.480218	-1.685966
18 H	3.640510	1.797236	-1.683038
19 H	3.760131	2.694765	-0.155768
20 H	2.654248	5.413870	-1.216638
21 H	2.150407	4.659520	0.316892
22 H	0.923175	5.105577	-0.897624
23 H	1.841526	2.430417	-3.418581
24 H	2.473661	4.096172	-3.424765
25 H	0.743117	3.798605	-3.093367
26 H	2.371775	-4.858243	2.222016
27 H	-0.075451	-5.068569	-0.649821
28 H	-0.572946	-4.107669	2.983628
29 H	-2.588535	-2.443824	2.109806
30 H	-4.787044	-1.240546	1.361993

31 H	-4.911140	0.533371	1.500800
32 H	-4.986689	-0.482533	2.960895
33 H	-2.881486	-1.760268	3.735048
34 H	2.726336	-3.386804	1.274074
35 H	1.840268	-3.256799	2.805845
36 H	-1.356487	-4.850134	1.564630
37 H	-2.149761	2.471638	1.955149
38 H	-0.040999	-5.711894	2.417561
39 H	-1.322369	-1.490448	2.903633
40 H	-2.566767	2.127087	-1.813355
41 O	0.697951	-1.643320	1.062454
42 C	0.040324	-2.702405	0.679503
43 C	0.646472	-4.063064	1.155238
44 C	-0.400192	-4.724480	2.089371
45 C	1.978795	-3.877890	1.911027
46 C	0.864335	-4.951849	-0.094702
47 O	-1.017759	-2.711482	0.008595
48 N	-2.354015	-0.066811	0.794727
49 C	-2.983182	-0.300037	2.143767
50 C	-2.405878	-1.579867	2.761279
51 C	-4.511396	-0.370787	1.976515
52 C	-2.248591	1.237740	0.143641
53 C	-2.668607	2.443277	0.990680
54 C	-2.862882	1.226492	-1.263752
55 H	-2.591459	-0.835978	0.149734

Four-membered cyclopalladation of palladium monoamine **TS-6**



Imaginary frequency at -1096 cm^{-1}.

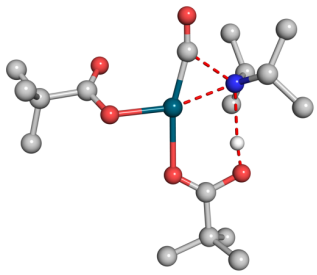
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-6745.33	318.154	211.583	-6510.36

Atom	X	Y	Z
1 Pd	-0.779419	0.304204	0.849814
2 O	0.738547	2.539457	-0.373730
3 C	1.600909	1.819395	0.248082
4 C	3.096934	2.156039	0.063103
5 C	3.973731	1.345463	1.040972

6 C	3.300677	3.674386	0.290483
7 C	3.453892	1.783619	-1.404150
8 O	1.293661	0.816371	0.977005
9 H	-5.272137	-1.477141	-1.364232
10 H	-4.046431	-2.359402	1.237183
11 H	2.888703	-2.557505	0.232440
12 H	-2.836238	-0.904701	-1.196877
13 H	-3.189504	1.569646	-0.893527
14 H	2.657402	-2.035772	-1.458593
15 H	-2.341898	-2.483706	0.745512
16 H	-5.587616	-0.616811	0.160386
17 H	5.028419	1.617401	0.892512
18 H	3.865280	0.267055	0.875772
19 H	3.701203	1.558363	2.083619
20 H	4.358678	3.928606	0.135173
21 H	3.026754	3.955161	1.318042
22 H	2.688926	4.261093	-0.406032
23 H	3.301624	0.710716	-1.584952
24 H	4.512094	2.017304	-1.589310
25 H	2.836120	2.351889	-2.111940
26 H	1.404099	-4.198202	-1.975667
27 H	2.122067	-0.992830	-0.113040
28 H	-1.094945	-2.467144	-1.519393
29 H	-1.774571	2.626378	1.627740
30 H	-4.247104	2.206140	1.935130
31 H	-5.265004	1.765948	0.536828
32 H	-4.364881	3.303107	0.541631
33 H	-1.710912	3.222921	-0.038921
34 H	1.672927	-4.731817	-0.292172
35 H	0.028034	-4.710686	-0.959987
36 H	-0.243980	-0.932075	-1.213671
37 H	-5.037245	0.278150	-1.285566
38 H	0.329207	-2.026129	-2.491754
39 H	-0.474986	2.151787	0.053094
40 H	-3.630219	-3.091680	-0.328357
41 O	-0.321299	-1.656282	1.494184
42 C	0.267861	-2.715311	0.973833
43 C	0.821907	-2.718368	-0.485460
44 C	-0.106797	-1.988799	-1.481572
45 C	0.992838	-4.183876	-0.954891
46 C	2.211246	-2.027034	-0.452106

47 O	0.402654	-3.729730	1.683527
48 N	-2.912382	0.132448	0.621016
49 C	-3.097431	1.585321	0.201345
50 C	-1.787513	2.309836	0.574393
51 C	-4.326083	2.244794	0.838159
52 C	-3.473367	-0.932344	-0.302266
53 C	-4.930025	-0.655123	-0.719696
54 C	-3.355149	-2.300101	0.381621
55 H	-3.314354	-0.005646	1.561617

Direct carbamoyl formation from palladium carbonyl amine dipivalate by 1,1 insertion of CO **TS-7** [Adam Smalley's work]



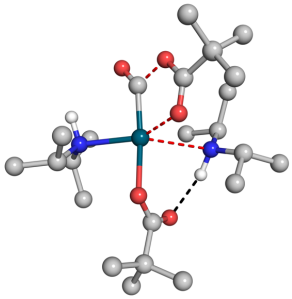
Imaginary frequency at -276 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7095.54	326.367	227.977	-6813.99

Atom	X	Y	Z
1 Pd	0.464836	-0.399039	0.066828
2 H	-1.762493	-6.335826	1.026468
3 H	-1.760676	-5.133169	-0.287308
4 H	-2.103934	0.953413	3.006638
5 H	-0.441703	2.551389	3.852447
6 H	-0.928575	3.061033	2.218497
7 H	0.633563	2.248158	2.470426
8 H	-2.625661	-4.788280	1.235275
9 C	-1.733712	-5.260124	0.804283
10 O	-1.473038	-2.485517	1.504236
11 N	-1.258762	0.465957	1.163785
12 C	-1.080394	0.897423	2.603150
13 C	-0.419071	2.277460	2.787866
14 C	-0.315143	-0.165628	3.413898
15 C	-2.597930	0.749250	0.513306
16 C	-3.663188	-0.271782	0.971703
17 H	-0.848151	-1.122711	3.439690
18 H	-0.182021	0.179564	4.448825

19 H	0.684061	-0.330991	2.984479
20 H	-2.428880	0.592331	-0.562577
21 H	-3.775504	-0.263563	2.065398
22 H	-3.416759	-1.291327	0.653972
23 H	-4.636021	-0.007370	0.532870
24 H	-4.031845	2.321826	0.120948
25 H	-3.367204	2.381805	1.764714
26 C	-3.114582	2.189557	0.712756
27 H	-1.353743	-1.494114	1.315855
28 H	-0.444673	-5.881033	3.198552
29 H	-1.314073	-4.334255	3.392410
30 H	0.471932	-4.364745	3.384874
31 H	0.775893	-6.416186	1.025589
32 C	4.820350	-1.721663	-1.490093
33 H	0.827856	-5.222631	-0.300204
34 H	-2.387524	2.937514	0.381039
35 O	0.559507	-2.618665	0.498644
36 C	-0.394655	-3.158014	1.083596
37 C	-0.433086	-4.654808	1.399200
38 C	-0.432033	-4.811492	2.946427
39 C	0.806020	-5.343455	0.790803
40 H	6.439445	0.472219	-1.990784
41 H	5.839891	0.580245	-0.310821
42 H	5.276310	1.746277	-1.523536
43 C	5.561470	0.697478	-1.366543
44 O	3.179337	0.946754	0.025930
45 H	4.882643	-0.259880	-3.871269
46 H	3.686620	0.978784	-3.411723
47 H	3.197655	-0.732650	-3.506263
48 H	5.694373	-1.974054	-2.109822
49 C	4.014354	-0.054874	-3.226652
50 H	5.092415	-1.875193	-0.435203
51 O	2.131798	-0.706053	-1.138120
52 C	3.156253	0.066668	-0.848502
53 C	4.402753	-0.249698	-1.739228
54 H	3.998043	-2.404810	-1.737474
55 H	1.733496	-4.919157	1.196965
56 C	-0.015218	1.420454	0.013395
57 O	-0.089756	2.546118	-0.295640

Palladium anhydride formation from palladium carbonyl amine dipivalate with external amine **TS-8**



Imaginary frequency at -70 cm^{-1}.

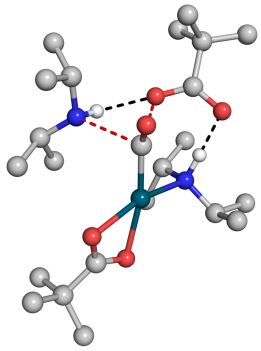
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9746.88	466.125	282.495	-9391.82

Atom	X	Y	Z
1 Pd	0.823574	0.348771	-0.467237
2 H	-0.355693	-5.432841	-0.116735
3 H	0.971957	-4.262421	0.081217
4 H	-2.449513	2.715206	1.871717
5 H	-1.253936	4.735415	1.019541
6 H	-2.228823	4.000202	-0.267216
7 H	-0.471052	3.750401	-0.243454
8 H	-0.233749	-4.012153	-1.196094
9 N	2.848150	-0.476733	0.172638
10 C	3.155702	-0.590816	1.654353
11 C	2.256505	-1.618056	2.345791
12 C	3.044317	0.789139	2.309948
13 C	3.117091	-1.727770	-0.648429
14 C	4.485175	-2.368423	-0.341705
15 C	3.004362	-1.384499	-2.141982
16 H	3.481762	0.254288	-0.184693
17 H	-0.410115	1.515407	2.809597
18 H	-0.385416	3.291602	2.987367
19 H	0.597054	2.508926	1.728149
20 H	-2.594528	1.891249	-1.323417
21 H	-4.144510	2.752074	0.450938
22 H	-4.343038	1.097532	1.083833
23 H	-4.954776	1.520926	-0.535701
24 H	-3.193683	-0.867003	-0.121659
25 H	-1.996945	-0.568757	-1.397100
26 H	4.205805	-0.915271	1.735781
27 H	2.582323	-1.737675	3.388728
28 H	2.303648	-2.601741	1.863631

29 H	1.212746	-1.283787	2.342507
30 H	3.404584	0.729655	3.346589
31 H	2.002353	1.120878	2.324400
32 H	3.637444	1.543612	1.775309
33 H	2.312239	-2.425852	-0.394606
34 H	4.553576	-2.746207	0.685451
35 H	5.301946	-1.649159	-0.507082
36 H	4.640662	-3.219818	-1.018870
37 H	3.759145	-0.635771	-2.430320
38 H	2.010060	-0.990266	-2.383640
39 H	3.172822	-2.288441	-2.743282
40 H	-3.723520	-0.266492	-1.713646
41 O	0.061634	-1.656237	-0.249431
42 C	-0.650702	-2.029493	0.766599
43 C	-0.968122	-3.560321	0.818783
44 C	-2.464375	-3.723710	0.445474
45 C	-0.732926	-4.065577	2.263080
46 C	-0.093729	-4.364489	-0.166775
47 O	-1.095188	-1.285014	1.670650
48 N	-1.614333	1.355596	0.451721
49 C	-1.526925	2.592255	1.271333
50 C	-1.363407	3.841059	0.388608
51 C	-0.359978	2.466214	2.260707
52 C	-2.795315	1.243383	-0.457016
53 C	-4.135200	1.688858	0.178492
54 C	-2.928052	-0.204887	-0.956716
55 H	-1.585232	0.525872	1.066777
56 H	-2.753865	-4.784758	0.494922
57 H	-2.654165	-3.359379	-0.574230
58 H	-3.095670	-3.153799	1.140797
59 H	-1.007773	-5.128620	2.340543
60 H	-1.334817	-3.486978	2.974861
61 H	0.323934	-3.962080	2.547406
62 C	1.649138	2.083324	-0.854011
63 O	2.546268	2.750054	-0.436582
64 H	0.915727	2.077357	-5.289451
65 O	0.917921	2.780511	-2.113491
66 H	-2.230334	2.185052	-5.355675
67 H	-0.636652	4.675306	-2.990363
68 H	-2.147482	3.783023	-2.694645
69 H	-1.836112	4.484405	-4.301123

70 H	1.153595	3.687634	-4.558632
71 H	-0.063611	3.457591	-5.845592
72 H	-1.270273	0.775018	-4.828366
73 C	-0.007961	2.021434	-2.696296
74 O	-0.307158	0.882736	-2.300890
75 C	-0.687574	2.677503	-3.910236
76 C	-1.738153	1.710402	-4.495101
77 C	-1.367291	3.990440	-3.437778
78 C	0.405565	2.995581	-4.965327
79 H	-2.500991	1.457471	-3.748107

Carbamoyl formation from palladium anhydride monoamine pivalate with external amine **TS-9** [Adam Smalley's work]



Imaginary frequency at -26 cm^{-1}

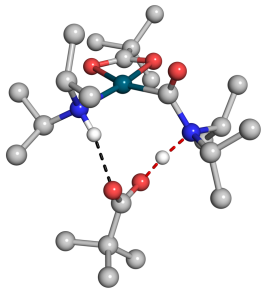
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9738.20	464.842	281.085	-9383.87

Atom	X	Y	Z
1 Pd	0.837668	-1.182234	0.758985
2 H	-1.126787	-4.125949	5.471661
3 H	-1.510476	-2.606139	4.619686
4 H	-4.076085	-0.646465	0.106571
5 H	-3.738212	-1.803446	2.295705
6 H	-3.508453	-0.054350	2.473989
7 H	-2.092427	-1.124867	2.405938
8 H	0.070809	-2.805970	5.408068
9 N	1.756128	-1.440457	-1.175556
10 C	3.120817	-2.055916	-0.984754
11 C	3.958762	-1.116356	-0.098545
12 C	3.849155	-2.305674	-2.323614
13 C	0.733054	-2.145740	-2.059689
14 C	0.954266	-1.911772	-3.574161
15 C	0.574310	-3.633288	-1.720185
16 H	1.884940	-0.453080	-1.547719

17 H	-2.583013	-2.132900	-1.245617
18 H	-3.247572	-2.997519	0.162176
19 H	-1.568509	-2.419623	0.190905
20 H	-1.793690	2.186115	-0.523739
21 H	-4.713348	1.262269	-0.795624
22 H	-3.502697	1.356755	-2.106660
23 H	-4.049569	2.837470	-1.281724
24 H	-3.133426	3.350142	1.123018
25 H	-3.940482	1.859803	1.647224
26 H	2.974363	-3.014564	-0.465577
27 H	4.956218	-1.548032	0.058173
28 H	3.492394	-0.966213	0.884132
29 H	4.069386	-0.135549	-0.582662
30 H	4.880698	-2.620120	-2.111690
31 H	3.879791	-1.384100	-2.920216
32 H	3.373866	-3.094493	-2.913602
33 H	-0.193767	-1.618220	-1.812973
34 H	1.676491	-2.613778	-4.005149
35 H	1.294189	-0.891468	-3.774820
36 H	-0.007807	-2.058655	-4.085514
37 H	1.458866	-4.213833	-2.015886
38 H	0.397844	-3.794814	-0.650525
39 H	-0.287131	-4.029790	-2.275663
40 H	-2.198435	2.088635	1.968474
41 O	0.086703	-1.618531	2.792642
42 C	0.412183	-2.851007	2.628025
43 C	-0.143594	-3.940455	3.543551
44 C	0.965563	-4.970713	3.862799
45 C	-1.287930	-4.621217	2.732582
46 C	-0.713089	-3.326387	4.840627
47 O	1.128258	-3.174478	1.604174
48 N	-2.141841	0.240823	0.004926
49 C	-3.050462	-0.844971	0.470828
50 C	-3.098263	-0.956066	2.007417
51 C	-2.585189	-2.176915	-0.146375
52 C	-2.651837	1.638372	-0.114177
53 C	-3.802294	1.775382	-1.135403
54 C	-3.002727	2.265000	1.242687
55 H	-1.767044	0.006705	-0.919052
56 H	0.544887	-5.789766	4.463351
57 H	1.778760	-4.503632	4.436459

58 H	1.387021	-5.390596	2.940340
59 H	-1.736516	-5.423707	3.335507
60 H	-0.898995	-5.052324	1.800341
61 H	-2.071689	-3.894348	2.481595
62 C	0.287834	0.662217	0.416091
63 O	0.316812	1.783819	0.712429
64 H	-1.531273	1.449512	-3.965170
65 O	-0.191183	0.827318	-1.886683
66 H	-0.443930	4.372292	-3.679033
67 H	2.108440	1.862768	-4.939462
68 H	2.442789	3.196442	-3.819273
69 H	1.394744	3.471872	-5.241381
70 H	-0.259759	0.826710	-5.042514
71 H	-0.947122	2.446000	-5.331873
72 H	0.576865	4.064575	-2.248301
73 C	0.798071	1.340007	-2.510973
74 O	2.017222	1.069646	-2.285113
75 C	0.428460	2.363685	-3.631913
76 C	-0.159794	3.616005	-2.930970
77 C	1.670758	2.748891	-4.458306
78 C	-0.647018	1.731226	-4.550037
79 H	-1.049686	3.344493	-2.349200

Deprotonation of protonated carbamoyl amine pivalate with external pivalate **TS-10** [Adam Smalley's work]



Imaginary frequency at -1072 cm^{-1}. Additional low intensity negative frequency observed at -19 cm^{-1} corresponding to pivalate rotation.

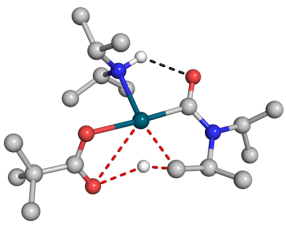
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9743.78	461.751	264.542	-9386.03

Atom	X	Y	Z
1 Pd	0.704359	-1.388413	0.615132
2 H	-1.761742	-4.840920	4.738604
3 H	-1.385198	-3.117833	4.450013
4 H	-2.484623	1.976645	1.122466

5 H	-2.469378	1.075773	3.374946
6 H	-0.864033	1.780108	3.067596
7 H	-1.093277	0.010006	3.022238
8 H	-0.074968	-4.324639	4.480745
9 N	2.022183	-1.003050	-1.101040
10 C	3.459058	-0.572027	-0.812716
11 C	3.930699	-1.009005	0.581952
12 C	3.599962	0.942487	-1.029874
13 C	1.902628	-2.162168	-2.084938
14 C	2.455311	-1.776577	-3.473288
15 C	2.545358	-3.452359	-1.556426
16 H	1.555740	-0.212247	-1.585167
17 H	-3.154244	-0.004149	-0.180977
18 H	-3.700631	-0.150119	1.512998
19 H	-2.292719	-1.076626	0.953591
20 H	0.511364	2.577987	-0.646805
21 H	-2.498782	3.234341	-0.556463
22 H	-1.663215	2.421068	-1.898015
23 H	-1.245120	4.090999	-1.472338
24 H	-0.022795	4.647623	0.620864
25 H	-1.212697	3.791108	1.616179
26 H	4.093078	-1.075933	-1.554426
27 H	5.003431	-0.787999	0.690030
28 H	3.785769	-2.086024	0.732321
29 H	3.383760	-0.466934	1.363485
30 H	4.649518	1.238952	-0.892916
31 H	2.991828	1.498890	-0.307307
32 H	3.286693	1.224861	-2.044693
33 H	0.817026	-2.315955	-2.180750
34 H	3.553000	-1.724631	-3.472657
35 H	2.054853	-0.809231	-3.798114
36 H	2.158421	-2.542029	-4.204030
37 H	3.634911	-3.343472	-1.463029
38 H	2.129434	-3.746991	-0.587794
39 H	2.353434	-4.264287	-2.272138
40 H	0.521577	3.384514	1.749276
41 O	-0.544784	-2.117958	2.209413
42 C	-0.428970	-3.369269	1.882627
43 C	-1.297899	-4.377091	2.657087
44 C	-0.909708	-5.821432	2.279865
45 C	-2.774365	-4.097433	2.258079

46 C	-1.117385	-4.147131	4.178630
47 O	0.328498	-3.722654	0.929812
48 N	-0.692593	1.200660	0.359675
49 C	-1.925666	1.049050	1.290134
50 C	-1.550641	0.976118	2.779020
51 C	-2.819441	-0.122050	0.855816
52 C	-0.431100	2.655321	-0.088093
53 C	-1.531429	3.112104	-1.063242
54 C	-0.274797	3.670002	1.056984
55 H	-0.933245	0.496976	-0.765216
56 H	-1.549631	-6.531895	2.823255
57 H	0.138475	-6.025052	2.538924
58 H	-1.029270	-5.990485	1.202060
59 H	-3.442431	-4.792272	2.787877
60 H	-2.919018	-4.235368	1.176525
61 H	-3.055243	-3.068048	2.517016
62 C	0.550652	0.561994	0.922542
63 O	1.403812	1.223733	1.473559
64 H	0.101722	1.435192	-5.239292
65 O	-1.284994	-0.068171	-1.775865
66 H	-1.458523	-1.313950	-5.740957
67 H	-3.245301	1.099250	-3.465898
68 H	-3.197507	-0.670468	-3.338456
69 H	-3.408488	0.103105	-4.934881
70 H	-1.323835	2.340345	-4.683293
71 H	-1.462273	1.252628	-6.088309
72 H	-1.105443	-1.973879	-4.121710
73 C	-0.624648	0.367062	-2.822217
74 O	0.516665	0.872085	-2.761880
75 C	-1.368462	0.208066	-4.175504
76 C	-0.908837	-1.134803	-4.804406
77 C	-2.900211	0.181146	-3.962116
78 C	-0.985650	1.382634	-5.105749
79 H	0.163174	-1.112914	-5.033038

C-H activation of palladium carbamoyl amine pivalate **TS-11**



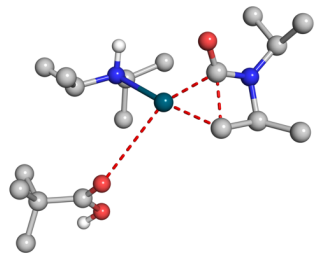
Imaginary frequency at -559 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7597.40	363.292	230.588	-7324.76

Atom	X	Y	Z
1 Pd	-0.266858	-0.280542	0.196564
2 O	0.162029	1.910045	0.303284
3 C	1.055026	2.212675	1.184245
4 C	1.260793	3.737430	1.459779
5 C	0.924193	3.993722	2.951511
6 C	0.349767	4.605708	0.566593
7 C	2.747081	4.080347	1.192628
8 O	1.741709	1.385515	1.842350
9 H	-4.549433	2.487327	-1.111912
10 H	-3.065980	0.040563	-2.223540
11 C	-2.485769	0.929182	-1.931307
12 H	-2.181218	2.202824	-0.223575
13 H	-3.904240	0.560615	1.899051
14 C	-2.814277	1.347174	-0.489956
15 H	-1.417730	0.697468	-2.039654
16 H	-4.946685	0.855515	-0.520361
17 H	1.096054	5.051647	3.202599
18 H	1.551597	3.366690	3.598993
19 H	-0.129853	3.759328	3.159914
20 H	0.511966	5.672175	0.787855
21 H	-0.708345	4.369228	0.740569
22 H	0.559506	4.430691	-0.497140
23 H	3.400327	3.445657	1.806007
24 H	2.944019	5.135836	1.435439
25 H	3.000463	3.918329	0.134104
26 H	3.581941	-3.030952	-1.006998
27 C	-4.300126	1.731004	-0.354511
28 H	1.547070	-0.960946	-1.287289
29 H	-1.042382	1.394325	2.651304
30 H	-1.474226	-1.113235	2.735495
31 H	-3.023347	-1.776400	2.171712
32 H	-2.957908	-0.819417	3.680433
33 H	-2.538808	1.729422	3.560874
34 H	2.650833	-4.516565	-0.756571
35 H	2.111208	-3.334839	-1.975529
36 H	1.357077	-0.352424	0.786673

37 H	-4.533417	2.157560	0.628707
38 H	2.843117	-0.819360	-0.086482
39 H	-2.250105	2.510523	1.989392
40 H	-2.731720	1.745517	-2.623787
41 C	-0.733386	-2.260771	0.025851
42 N	0.315103	-3.144944	0.099213
43 C	1.728204	-2.686779	0.071917
44 C	1.825237	-1.195498	-0.250354
45 C	2.565522	-3.449096	-0.981421
46 H	-2.837323	-0.652880	0.104903
47 O	-1.914772	-2.625300	-0.089311
48 N	-2.403829	0.224757	0.440321
49 C	-2.816111	0.387794	1.892006
50 C	-2.118424	1.581464	2.556224
51 C	-2.552715	-0.914845	2.663362
52 C	-0.034470	-4.590383	0.335958
53 C	-0.168161	-5.377161	-0.980826
54 C	0.889570	-5.258114	1.367645
55 H	2.166418	-2.854714	1.068471
56 H	-1.036488	-4.541832	0.782640
57 H	-0.844317	-4.843674	-1.661604
58 H	-0.595173	-6.370217	-0.775610
59 H	0.798090	-5.518454	-1.479697
60 H	1.911402	-5.408122	0.998432
61 H	0.478319	-6.247152	1.614139
62 H	0.933298	-4.667509	2.292842

Reductive elimination from carbamoyl palladacycle amine pivalic acid **TS-12**



Imaginary frequency at -356 cm^{-1}.

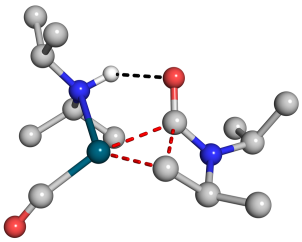
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7562.60	364.122	235.052	-7290.89

Atom	X	Y	Z
1 Pd	-1.134683	-1.106832	-0.349928
2 O	1.330786	1.414616	-0.238289

3 C	1.922036	2.220289	0.452597
4 C	1.754743	3.755404	0.369061
5 C	1.027924	4.248241	1.651601
6 C	0.909931	4.096408	-0.877733
7 C	3.145406	4.437555	0.259649
8 O	2.788919	1.748895	1.418039
9 H	-2.606874	3.834824	1.127830
10 H	-3.633619	1.658122	-0.783800
11 C	-2.558424	1.898019	-0.793193
12 H	-0.901274	2.043142	0.557795
13 H	-2.220543	0.801213	3.195713
14 C	-1.970099	1.818118	0.622944
15 H	-2.052182	1.185088	-1.459174
16 H	-3.720182	2.567519	1.697796
17 H	0.926316	5.342318	1.612403
18 H	1.582766	3.990307	2.564547
19 H	0.023314	3.816094	1.728436
20 H	0.763476	5.183768	-0.935984
21 H	-0.071085	3.611327	-0.835823
22 H	1.411248	3.757565	-1.793915
23 H	3.755121	4.295182	1.165139
24 H	3.009579	5.520144	0.128498
25 H	3.709120	4.049900	-0.599793
26 H	1.386088	-5.240232	-1.772209
27 C	-2.658073	2.826052	1.562891
28 H	-0.297607	-3.033363	-2.644170
29 H	0.470553	-0.031789	1.964873
30 H	-1.335607	-1.990649	2.285195
31 H	-2.992036	-1.540552	2.745196
32 H	-1.696079	-1.477142	3.966468
33 H	0.191386	0.188365	3.720527
34 H	0.280062	-6.234518	-0.792291
35 H	-0.295554	-5.502512	-2.315059
36 H	-2.353194	-6.431289	-1.453520
37 H	-2.185409	2.866991	2.552857
38 H	0.518444	-2.026026	-1.395983
39 H	0.055183	1.565949	2.614116
40 H	-2.439481	2.912791	-1.197811
41 C	-1.964748	-2.977894	-0.992413
42 N	-1.498708	-4.063985	-0.256474
43 C	-0.076325	-4.078751	-0.681057

44 C	-0.233858	-2.826818	-1.569346
45 C	0.344324	-5.344946	-1.435439
46 H	-3.045064	0.118982	1.049875
47 O	-3.093461	-2.826863	-1.477305
48 N	-2.050268	0.387552	1.100904
49 C	-1.622410	0.152617	2.531364
50 C	-0.137383	0.491313	2.716091
51 C	-1.929833	-1.304822	2.905712
52 C	-2.300422	-5.150962	0.327482
53 C	-3.267801	-4.572635	1.380816
54 C	-3.052154	-5.981178	-0.737937
55 H	0.599429	-3.909416	0.174434
56 H	-1.574954	-5.802197	0.841734
57 H	-2.710793	-4.041565	2.162151
58 H	-3.855363	-5.377591	1.845464
59 H	-3.956473	-3.863523	0.902652
60 H	-3.745941	-5.332810	-1.288182
61 H	-3.623235	-6.788482	-0.255196
62 H	3.232059	2.504422	1.867561

Reductive elimination from carbamoyl palladacycle amine carbon monoxide **TS-13**



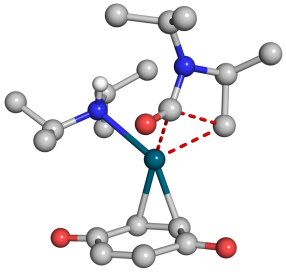
Imaginary frequency at -351 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-5788.42	272.591	197.808	-5593.60

Atom	X	Y	Z
1 Pd	-0.648943	-0.573685	-0.297677
2 C	0.793923	0.738707	-0.000580
3 O	-2.997723	-2.220407	-0.669937
4 N	-2.535915	0.243128	1.146317
5 C	-2.266655	0.295403	2.618385
6 C	-1.280121	1.419895	2.966250
7 C	-1.737650	-1.075260	3.063023
8 C	-1.847093	-4.821660	0.286762
9 H	-4.910769	2.767218	0.760966
10 H	-4.169837	0.334159	-1.048627

11 C	-3.472064	1.177067	-0.940031
12 H	-2.438652	2.265528	0.600347
13 H	-3.209794	0.481733	3.165983
14 C	-3.182511	1.456486	0.543775
15 H	-2.547089	0.914995	-1.472949
16 H	-5.205467	1.088666	1.283833
17 C	-2.444726	-4.475681	1.662422
18 C	-2.908600	-5.419800	-0.662174
19 H	0.955669	-3.521699	-0.489574
20 H	-1.042511	-5.557958	0.437635
21 H	-1.672285	-4.066460	2.325310
22 H	-2.871172	-5.376693	2.126006
23 H	-3.241781	-3.730058	1.548828
24 H	-3.691596	-4.677251	-0.860017
25 H	-3.367069	-6.305702	-0.198269
26 H	1.119198	-4.688213	-2.666620
27 C	-4.464909	1.904041	1.276839
28 H	-0.885096	-2.481298	-2.749054
29 H	-0.331302	1.278193	2.433210
30 H	-0.809734	-1.322151	2.525563
31 H	-2.471709	-1.863081	2.854169
32 H	-1.532650	-1.074883	4.143232
33 H	-1.077316	1.410971	4.046737
34 H	0.330674	-5.764406	-1.489969
35 H	-0.647320	-4.922794	-2.725610
36 H	-2.463827	-5.722900	-1.617109
37 H	-4.268466	2.201758	2.315069
38 H	0.559186	-1.670008	-2.093465
39 H	-1.676252	2.411250	2.709771
40 H	-3.912274	2.065500	-1.414506
41 C	-1.784809	-2.455784	-0.653242
42 N	-1.173153	-3.635112	-0.287971
43 C	0.058767	-3.619849	-1.122588
44 C	-0.290681	-2.315745	-1.840332
45 C	0.216644	-4.827752	-2.054231
46 H	-3.159602	-0.556522	0.962689
47 O	1.701899	1.275618	0.495492

Reductive elimination from carbamoyl palladacycle amine 1,4-benzoquinone **TS-14**



Imaginary frequency at -280 cm^{-1}.

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7239.41	326.261	221.109	-7000.08

Atom	X	Y	Z
1 Pd	-0.209762	-0.471402	0.469165
2 C	1.982752	0.187732	-1.293356
3 O	-1.365808	-1.829372	-1.776893
4 C	-1.771561	0.900352	3.392232
5 C	-2.079242	-1.608706	3.182082
6 C	-2.787913	-4.126747	-0.407445
7 C	-4.019054	-3.203119	-0.353923
8 N	-2.445236	-0.146492	1.216027
9 H	-4.857840	2.280049	0.536494
10 H	-3.779062	0.114384	-1.233712
11 C	-3.067136	0.903051	-0.945060
12 H	-2.371353	1.919115	0.815716
13 H	-3.624384	-0.132579	2.995794
14 C	-3.047627	1.087244	0.579019
15 H	-2.083094	0.619591	-1.332154
16 H	-5.143047	0.570240	0.944015
17 C	-2.635285	-4.810344	-1.780686
18 H	-0.715066	-3.757365	1.892885
19 H	-2.895076	-4.896626	0.371686
20 H	-4.151450	-2.786153	0.653856
21 H	-4.927276	-3.765283	-0.611786
22 H	-3.906526	-2.380445	-1.071954
23 H	-2.498698	-4.053778	-2.563745
24 H	-3.535336	-5.398783	-2.009580
25 C	-2.561295	-0.227675	2.716077
26 H	0.892173	-5.499681	1.133582
27 C	-4.461080	1.421493	1.096438
28 H	1.235941	-3.035327	-0.400292
29 H	-0.705956	0.818675	3.137758

30 H	-1.002464	-1.720918	2.996342
31 H	-2.606235	-2.414539	2.651927
32 H	-2.262558	-1.728130	4.259144
33 H	-1.878992	0.824520	4.483489
34 H	-0.768190	-5.995736	0.728666
35 H	0.304883	-5.347613	-0.544687
36 H	-1.768982	-5.482888	-1.789798
37 H	-4.469436	1.688070	2.160803
38 H	1.100118	-2.270876	1.222706
39 H	-2.121578	1.893664	3.084056
40 H	-3.373588	1.841270	-1.425717
41 C	-1.052721	-2.305193	-0.698257
42 N	-1.570623	-3.368879	-0.022984
43 C	-0.445666	-3.831716	0.829146
44 C	0.547958	-2.747885	0.402779
45 C	0.018116	-5.259237	0.511887
46 H	-2.959209	-0.953740	0.839386
47 C	0.864288	1.521547	0.523595
48 C	1.763829	0.503578	0.129118
49 C	0.133098	2.309881	-0.479086
50 C	0.347469	1.951012	-1.908495
51 C	1.192049	0.970604	-2.283414
52 O	2.797899	-0.679986	-1.671122
53 O	-0.635704	3.245881	-0.171345
54 H	0.881683	1.934493	1.533685
55 H	2.506920	0.106347	0.824223
56 H	-0.222502	2.534999	-2.632564
57 H	1.349666	0.709024	-3.330915

A1.3C $\Delta G_{50\%}$ values for intermediates and transition states

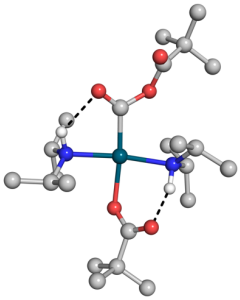
Entropy corrected Gibbs free energies ($\Delta G_{50\%}$) values were obtained by halving the raw entropy of each structure before calculating the Gibbs free energy.

	Gibbs energy kcalmol^{-1}	
	No entropy correction	*$\Delta G_{50\%}$ entropy correction*
Int-9	0.00	0.00
Int-10	10.63	19.97
***cis*-Int-11**	5.59	7.75
Int-12	26.59	17.80
Int-13a	15.70	9.16
Int-14a	34.68	28.35
Int-15	33.48	23.53
Int-16a	9.91	11.46
Int-17	22.91	25.55
Int-18	3.85	6.89
Int-19	–10.69	1.16
Int-20	17.00	17.91
TS-4	31.67	34.95
TS-5	34.25	43.59
TS-6	45.86	53.72
TS-7	45.15	46.57
TS-8	30.06	22.07
TS-9	38.01	29.74
TS-10	35.85	24.32
TS-11	25.55	26.21
TS-12	59.43	60.96
TS-13	32.89	36.30
TS-14	33.39	33.75

A1.3D Anhydride geometries

Calculations in this section were performed as previously, with the exception that DFT vibrational analysis was performed using a TZP basis set for palladium and DZP for all other atoms. Hydrogen bonding is shown in dotted lines for clarity.

Bisamine palladium anhydride pivalate **Int-13a**



DZP:

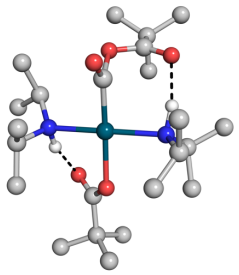
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9691.57	465.920	284.885	-9337.65

Atom	X	Y	Z
1 Pd	0.496087	-0.086359	-0.006798
2 H	1.002255	-5.667103	2.079311
3 H	0.688844	-4.035198	2.734615
4 H	-2.788138	0.999775	2.025811
5 H	-1.051783	1.439750	3.667236
6 H	-0.501746	2.062098	2.087033
7 H	0.158204	0.536982	2.718827
8 H	1.813693	-4.237407	1.382489
9 N	2.572119	-0.535848	-0.582666
10 C	3.589481	-0.334172	0.527695
11 C	3.437791	-1.387282	1.632580
12 C	3.476354	1.094540	1.081812
13 C	2.645337	-1.870802	-1.302811
14 C	4.060911	-2.183474	-1.820982
15 C	1.621829	-1.876239	-2.449707
16 H	2.752250	0.199403	-1.286121
17 H	-2.980145	-1.507824	2.231368
18 H	-2.427643	-0.756874	3.753681
19 H	-1.261416	-1.582172	2.685653
20 H	-2.519520	1.879455	-0.200975
21 H	-4.360540	0.443715	0.825644
22 H	-4.088056	-0.764680	-0.455039
23 H	-4.717297	0.852811	-0.862752

24 H	-2.067445	-0.494679	-2.098388
25 H	-2.955399	0.980527	-2.566324
26 H	4.588903	-0.434042	0.073066
27 H	4.154390	-1.169417	2.436543
28 H	3.639606	-2.401343	1.266627
29 H	2.420991	-1.379480	2.043854
30 H	4.299899	1.277835	1.785984
31 H	2.525169	1.233533	1.613964
32 H	3.531872	1.842528	0.279170
33 H	2.343020	-2.622428	-0.564815
34 H	4.788305	-2.303983	-1.008921
35 H	4.414275	-1.386309	-2.493167
36 H	4.039607	-3.123065	-2.390038
37 H	1.835894	-1.072332	-3.170126
38 H	0.601217	-1.743029	-2.070472
39 H	1.666854	-2.836582	-2.981388
40 H	-1.238038	1.084736	-2.155865
41 O	0.407317	-2.138136	0.803276
42 C	-0.516481	-2.958250	0.422413
43 C	-0.295663	-4.448410	0.820978
44 C	0.018406	-5.217388	-0.489249
45 C	-1.602976	-4.988067	1.449612
46 C	0.875018	-4.606178	1.814213
47 O	-1.540828	-2.649106	-0.240727
48 N	-1.622066	0.101414	0.498301
49 C	-1.886507	0.373328	1.975420
50 C	-0.747550	1.155634	2.648081
51 C	-2.160065	-0.952046	2.705458
52 C	-2.581013	0.811149	-0.437561
53 C	-4.023835	0.305701	-0.209051
54 C	-2.175929	0.581349	-1.902158
55 H	-1.778681	-0.913367	0.312154
56 H	0.158168	-6.288414	-0.277714
57 H	0.940244	-4.835373	-0.953258
58 H	-0.803417	-5.100807	-1.208349
59 H	-1.496178	-6.055574	1.694381
60 H	-2.441536	-4.861316	0.753523
61 H	-1.841666	-4.443984	2.376098
62 C	0.755582	1.743105	-0.780483
63 O	1.554233	2.071261	-1.632247
64 H	-2.291385	5.887531	-1.568656

65 O	-0.097131	2.761303	-0.175081
66 H	-2.545202	5.342535	1.493879
67 H	1.033848	5.686584	0.275889
68 H	0.464856	4.564997	1.536969
69 H	-0.128914	6.247452	1.504179
70 H	-0.627886	6.509133	-1.545532
71 H	-1.778894	7.006334	-0.275434
72 H	-3.072883	4.213721	0.223189
73 C	-0.588622	3.819841	-0.938512
74 O	-0.701219	3.781918	-2.145639
75 C	-1.026053	4.983188	-0.025799
76 C	-2.220509	4.513200	0.849151
77 C	0.165065	5.391160	0.880950
78 C	-1.458376	6.170306	-0.911999
79 H	-1.939757	3.668114	1.487772

Bisamine palladium anhydride pivalate **Int-13b**



DZP:

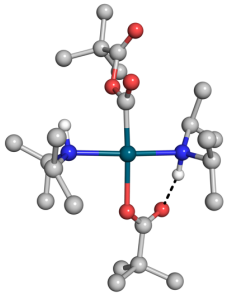
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9690.98	467.005	287.342	-9336.94

Atom	X	Y	Z
1 Pd	0.277451	-0.513773	0.211321
2 H	0.624569	-5.800939	2.987284
3 H	0.592171	-4.039518	3.280722
4 H	-2.976764	0.523452	2.501679
5 H	-1.211930	1.627788	3.811737
6 H	-1.075282	2.173955	2.121062
7 H	0.053694	0.960290	2.746433
8 H	1.520821	-4.694520	1.919451
9 N	2.237542	-0.961969	-0.688916
10 C	3.449160	-0.778432	0.209023
11 C	3.191176	-1.269936	1.641471
12 C	3.864303	0.700497	0.191171
13 C	2.224240	-2.225142	-1.557834

14 C	3.144092	-2.029121	-2.778407
15 C	2.559353	-3.509067	-0.792365
16 H	2.264806	-0.196145	-1.379795
17 H	-2.468328	-1.853359	3.017464
18 H	-1.909302	-0.783600	4.329818
19 H	-0.738751	-1.469685	3.170781
20 H	-2.369743	0.145445	-1.039482
21 H	-4.585974	-0.133125	1.083056
22 H	-4.017374	-1.414492	-0.023244
23 H	-4.831765	0.036745	-0.669017
24 H	-3.563212	2.257639	-0.752788
25 H	-3.368422	2.207238	1.010141
26 H	4.266769	-1.371921	-0.229406
27 H	4.131784	-1.247667	2.210485
28 H	2.782285	-2.284244	1.665688
29 H	2.467467	-0.610905	2.141404
30 H	4.769499	0.838923	0.798666
31 H	3.069827	1.332584	0.609186
32 H	4.077083	1.043545	-0.831255
33 H	1.186865	-2.299140	-1.911257
34 H	4.192736	-1.910794	-2.468394
35 H	2.845939	-1.147279	-3.358680
36 H	3.083472	-2.913531	-3.428715
37 H	3.609379	-3.528985	-0.468478
38 H	1.909627	-3.620783	0.075291
39 H	2.402400	-4.366463	-1.461896
40 H	-1.948451	2.416394	-0.047197
41 O	0.237146	-2.519021	1.076427
42 C	-0.792623	-3.294223	0.955081
43 C	-0.655364	-4.704989	1.607668
44 C	-0.576229	-5.734399	0.448939
45 C	-1.923671	-4.972678	2.456562
46 C	0.598620	-4.813573	2.500985
47 O	-1.866109	-2.994673	0.373322
48 N	-1.774919	-0.225626	0.925844
49 C	-1.940903	0.170795	2.381797
50 C	-0.988650	1.306848	2.783608
51 C	-1.752317	-1.062980	3.278648
52 C	-2.776159	0.383961	-0.049120
53 C	-4.135688	-0.329423	0.099498
54 C	-2.910295	1.906170	0.058261

55 H	-1.960466	-1.248000	0.838885
56 H	-0.513440	-6.755903	0.854318
57 H	0.312626	-5.557488	-0.173438
58 H	-1.467604	-5.660445	-0.188423
59 H	-1.892750	-5.993036	2.868456
60 H	-2.826285	-4.860636	1.842931
61 H	-1.987154	-4.266318	3.297160
62 C	0.392153	1.370825	-0.424278
63 O	0.733869	2.413558	0.031967
64 H	1.291637	0.341138	-5.371865
65 O	-0.366535	1.491356	-1.874185
66 H	-1.391192	-1.240042	-4.734716
67 H	-1.645900	2.507058	-4.250087
68 H	-2.432948	1.228704	-3.299690
69 H	-2.382023	1.109334	-5.077348
70 H	0.550633	1.947236	-5.560726
71 H	-0.233938	0.518280	-6.283381
72 H	-1.260041	-1.051570	-2.964263
73 C	0.364846	1.056767	-2.898781
74 O	1.590235	0.886561	-2.851641
75 C	-0.480074	0.654318	-4.124948
76 C	-0.752164	-0.866338	-3.921547
77 C	-1.818689	1.423660	-4.187339
78 C	0.336555	0.878588	-5.415932
79 H	0.189523	-1.430424	-3.929519

Bisamine palladium anhydride pivalate **Int-13c**



DZP:

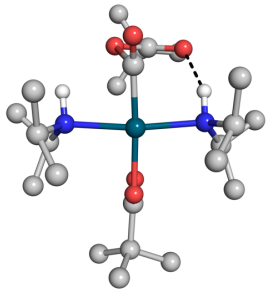
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9685.19	465.964	285.377	-9331.42

Atom	X	Y	Z
1 Pd	0.358370	-0.942742	0.237022
2 H	-1.963748	-4.761155	4.242060
3 H	-2.372434	-3.383026	3.190489

4 H	-2.828287	1.157203	1.857271
5 H	-1.092252	2.754649	2.755743
6 H	-1.301875	2.914992	0.995733
7 H	0.109486	2.042145	1.648423
8 H	-0.812556	-3.409970	4.031085
9 N	2.113330	-2.153917	-0.186730
10 C	3.254475	-2.068276	0.808888
11 C	2.920823	-2.924140	2.042291
12 C	3.574021	-0.619063	1.205588
13 C	2.506910	-2.266349	-1.653361
14 C	3.484973	-1.185465	-2.126026
15 C	3.034771	-3.685430	-1.945705
16 H	1.585001	-3.039462	-0.002306
17 H	-1.829414	-0.946866	2.946683
18 H	-1.661903	0.545409	3.914426
19 H	-0.276328	-0.115988	3.003703
20 H	-2.284641	-0.986113	-1.056417
21 H	-3.868518	-1.027376	1.581265
22 H	-2.622207	-2.209369	1.094817
23 H	-4.131315	-2.051874	0.155127
24 H	-4.526046	0.063773	-1.276421
25 H	-4.196073	1.138927	0.099772
26 H	4.142304	-2.501730	0.321452
27 H	3.754577	-2.884840	2.757193
28 H	2.744130	-3.971071	1.763169
29 H	2.015753	-2.547421	2.537477
30 H	4.475284	-0.601115	1.835621
31 H	2.739386	-0.190368	1.778074
32 H	3.742580	0.023731	0.335976
33 H	1.560502	-2.137798	-2.196328
34 H	4.473904	-1.305456	-1.662239
35 H	3.126879	-0.172764	-1.921961
36 H	3.614471	-1.276298	-3.213812
37 H	3.983893	-3.874526	-1.423893
38 H	2.303482	-4.442483	-1.631325
39 H	3.216456	-3.798818	-3.024047
40 H	-3.244184	1.287478	-1.402606
41 O	-0.415928	-2.548257	1.555639
42 C	-0.267689	-3.804565	1.303386
43 C	-0.920465	-4.784618	2.328318
44 C	0.186841	-5.740628	2.839158

45 C	-2.005979	-5.593773	1.573367
46 C	-1.555089	-4.036980	3.520137
47 O	0.362707	-4.292060	0.326586
48 N	-1.520904	0.234822	0.450227
49 C	-1.754092	0.922520	1.791805
50 C	-0.961849	2.238938	1.794698
51 C	-1.363642	0.040187	2.984133
52 C	-2.718942	-0.462775	-0.191685
53 C	-3.368985	-1.502241	0.724880
54 C	-3.728083	0.574479	-0.719052
55 H	-1.325702	1.004235	-0.201752
56 H	-0.242398	-6.489369	3.521963
57 H	0.962057	-5.181764	3.384459
58 H	0.663400	-6.255752	1.995024
59 H	-2.462471	-6.337556	2.243909
60 H	-1.563800	-6.113738	0.712884
61 H	-2.802756	-4.929490	1.205859
62 C	0.995508	0.595172	-0.860925
63 O	1.634305	1.578558	-0.586953
64 H	1.545102	1.051944	-6.022524
65 O	0.381462	0.418709	-2.188353
66 H	-0.497170	-1.247287	-5.588561
67 H	-1.555291	2.081164	-4.056072
68 H	-1.848772	0.466829	-3.358431
69 H	-2.104624	0.745928	-5.100299
70 H	0.454197	2.412853	-5.687197
71 H	-0.119656	1.035655	-6.667605
72 H	-0.266261	-1.462487	-3.831336
73 C	0.895416	0.996523	-3.351477
74 O	1.920233	1.640745	-3.411172
75 C	-0.002627	0.602525	-4.542082
76 C	0.103013	-0.937830	-4.721023
77 C	-1.471168	1.000155	-4.238483
78 C	0.502593	1.322129	-5.808647
79 H	1.145219	-1.240247	-4.897972

Bisamine palladium anhydride pivalate **Int-13d**



DZP:

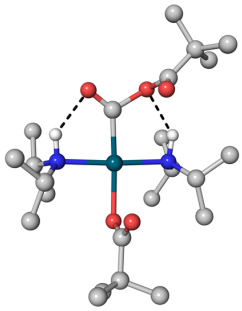
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9685.22	467.234	287.979	-9331.20

Atom	X	Y	Z
1 Pd	0.392273	-0.706869	0.182893
2 H	-1.112013	-5.638732	3.160248
3 H	-1.623790	-3.942958	2.976768
4 H	-3.098178	0.595029	1.950815
5 H	-1.887711	2.590713	2.752468
6 H	-2.074395	2.660943	0.985203
7 H	-0.502558	2.219249	1.704173
8 H	0.104408	-4.336273	3.027463
9 N	2.432729	-1.256290	-0.416584
10 C	3.560479	-0.871523	0.526929
11 C	3.147614	-1.030700	1.998023
12 C	4.044025	0.553495	0.223966
13 C	2.546510	-2.645428	-1.043229
14 C	3.588256	-2.616697	-2.178335
15 C	2.841809	-3.739557	-0.015406
16 H	2.462988	-0.620399	-1.233262
17 H	-1.524862	-1.193292	2.940560
18 H	-1.705811	0.276010	3.940238
19 H	-0.246469	0.027117	2.944681
20 H	-2.210042	-1.578311	-0.808803
21 H	-3.981820	-1.350117	1.695683
22 H	-2.572345	-2.424705	1.520198
23 H	-3.983587	-2.627543	0.465425
24 H	-4.552836	-0.820260	-1.284389
25 H	-4.373612	0.509067	-0.113737
26 H	4.392729	-1.559822	0.320021
27 H	4.022647	-0.881051	2.647178
28 H	2.724510	-2.020440	2.198293

29 H	2.389516	-0.279034	2.260529
30 H	4.925299	0.779732	0.840865
31 H	3.270199	1.294741	0.454919
32 H	4.325152	0.662622	-0.832767
33 H	1.555979	-2.832883	-1.475012
34 H	3.614458	-3.598377	-2.673310
35 H	4.596946	-2.406498	-1.792708
36 H	3.325613	-1.856626	-2.925320
37 H	3.867696	-3.672906	0.373882
38 H	2.140792	-3.688264	0.820727
39 H	2.729982	-4.717702	-0.500063
40 H	-3.379919	0.478425	-1.599640
41 O	-0.038779	-2.582770	1.132980
42 C	-0.503562	-3.543654	0.376548
43 C	-0.865345	-4.869921	1.136079
44 C	0.191125	-5.939148	0.747608
45 C	-2.253354	-5.357861	0.649115
46 C	-0.872792	-4.683262	2.667984
47 O	-0.657615	-3.482003	-0.858584
48 N	-1.690183	-0.003188	0.480221
49 C	-2.005942	0.637858	1.825771
50 C	-1.589901	2.114956	1.808061
51 C	-1.335384	-0.117025	2.982220
52 C	-2.749622	-0.962222	-0.081036
53 C	-3.351744	-1.889974	0.975698
54 C	-3.827489	-0.143800	-0.811175
55 H	-1.684742	0.759362	-0.208297
56 H	-0.117639	-6.922074	1.135182
57 H	1.174500	-5.703070	1.171480
58 H	0.285301	-6.003790	-0.344551
59 H	-2.464958	-6.352903	1.068623
60 H	-2.270624	-5.419221	-0.446276
61 H	-3.053192	-4.679850	0.969677
62 C	0.726583	1.113324	-0.559883
63 O	1.083411	2.210436	-0.378198
64 H	1.318140	-1.983003	-4.417673
65 O	-0.281837	0.975865	-2.238451
66 H	-1.711238	-1.937987	-4.459706
67 H	-0.098272	1.356777	-5.539571
68 H	-1.565912	1.268727	-4.531516
69 H	-1.384536	0.190528	-5.944048

70 H	1.662138	-0.548010	-5.403980
71 H	0.367058	-1.676925	-5.896619
72 H	-2.037063	-0.790389	-3.132909
73 C	0.515197	0.297216	-3.016675
74 O	1.744108	0.147896	-2.808771
75 C	-0.177672	-0.398074	-4.222005
76 C	-1.251718	-1.359550	-3.643612
77 C	-0.849113	0.674806	-5.113758
78 C	0.859140	-1.200294	-5.035417
79 H	-0.815225	-2.060367	-2.918933

Bisamine palladium anhydride pivalate **Int-13e**



DZP:

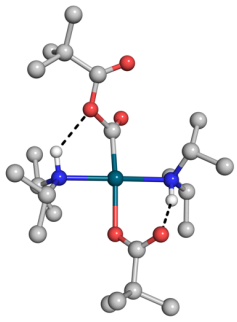
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9682.10	466.415	281.747	-9326.45

Atom	X	Y	Z
1 Pd	-0.036314	-1.013960	0.086611
2 H	0.541505	-6.971463	2.167925
3 H	1.637517	-5.697917	1.591028
4 H	-2.742473	0.508893	2.747082
5 H	-1.343580	2.569667	2.721326
6 H	-2.209590	2.363223	1.176262
7 H	-0.476037	1.975241	1.283913
8 H	0.351520	-6.308613	0.518030
9 N	1.890236	-1.492227	-0.816144
10 C	3.112450	-1.057887	-0.014700
11 C	3.006544	-1.402994	1.478501
12 C	3.321688	0.451699	-0.210227
13 C	1.949684	-2.876634	-1.475009
14 C	2.689670	-2.773613	-2.819036
15 C	2.550433	-3.950672	-0.568305
16 H	1.849833	-0.830795	-1.598854
17 H	-0.814013	-1.117150	3.401048

18 H	-0.774925	0.495984	4.168229
19 H	0.300392	0.112354	2.801392
20 H	-2.729702	-2.159233	0.270541
21 H	-3.465038	-1.518871	3.189142
22 H	-2.145401	-2.592464	2.659627
23 H	-3.828771	-2.991824	2.269478
24 H	-5.148176	-1.548458	0.621453
25 H	-4.655203	-0.014868	1.378927
26 H	3.979477	-1.584070	-0.445246
27 H	3.977321	-1.211717	1.958939
28 H	2.719553	-2.441721	1.653284
29 H	2.250144	-0.772789	1.962733
30 H	4.190345	0.783357	0.374700
31 H	2.439632	1.009767	0.134342
32 H	3.496296	0.702988	-1.263425
33 H	0.899626	-3.138528	-1.658071
34 H	2.746037	-3.764306	-3.292610
35 H	3.716652	-2.403260	-2.683654
36 H	2.156926	-2.107839	-3.508038
37 H	3.630141	-3.810879	-0.416760
38 H	2.053758	-3.956732	0.400844
39 H	2.396272	-4.932920	-1.033750
40 H	-4.298816	-0.320885	-0.345424
41 O	0.108863	-2.686676	1.507166
42 C	-0.429903	-3.794910	1.087576
43 C	-0.387124	-4.992622	2.107962
44 C	-1.796910	-5.631998	2.187132
45 C	0.071289	-4.540582	3.510754
46 C	0.600376	-6.057137	1.558004
47 O	-0.945349	-3.969132	-0.037346
48 N	-1.917106	-0.365445	0.998322
49 C	-1.763560	0.499100	2.243345
50 C	-1.430921	1.939602	1.825495
51 C	-0.704663	-0.046339	3.214126
52 C	-3.017702	-1.430608	1.039829
53 C	-3.110089	-2.169320	2.377799
54 C	-4.358260	-0.784343	0.650360
55 H	-2.211952	0.282613	0.255589
56 H	-1.762178	-6.535947	2.814039
57 H	-2.146103	-5.906784	1.183442
58 H	-2.526077	-4.941956	2.629059

59 H	0.119308	-5.407571	4.188206
60 H	-0.624087	-3.807606	3.942074
61 H	1.062540	-4.070837	3.466803
62 C	-0.346739	0.472111	-1.242897
63 O	-1.296634	1.200006	-1.366844
64 H	0.399413	-0.401562	-6.201577
65 O	0.762071	0.736070	-2.314718
66 H	1.351264	2.584808	-5.811045
67 H	3.326153	0.052743	-3.798410
68 H	2.878511	1.707167	-3.309632
69 H	3.467416	1.389355	-4.960633
70 H	1.884175	-1.168057	-5.600665
71 H	1.995116	0.251390	-6.670384
72 H	0.712601	2.772077	-4.152886
73 C	0.528356	0.144089	-3.523677
74 O	-0.299913	-0.739478	-3.691611
75 C	1.414538	0.745834	-4.636443
76 C	0.757857	2.102066	-5.021626
77 C	2.859679	0.987997	-4.136747
78 C	1.420245	-0.204762	-5.852083
79 H	-0.262659	1.946372	-5.398004

Bisamine palladium anhydride pivalate **Int-13f**



DZP:

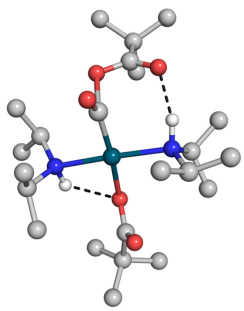
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9684.69	466.809	291.081	9332.32

Atom	X	Y	Z
1 Pd	0.123311	-1.219263	-0.019558
2 H	1.576212	-4.891315	4.511376
3 H	1.135865	-3.199505	4.147085
4 H	-3.330513	-0.097801	1.918393
5 H	-1.861836	1.700109	2.717209
6 H	-1.753036	1.633388	0.935513
7 H	-0.448547	0.955614	1.921023

8 H	2.221853	-4.085150	3.061315
9 N	2.121143	-1.640315	-0.875324
10 C	3.293352	-0.871602	-0.285900
11 C	3.175055	-0.740641	1.239409
12 C	3.387706	0.503805	-0.963766
13 C	2.354965	-3.131918	-1.140798
14 C	3.122275	-3.305666	-2.464250
15 C	3.035830	-3.865789	0.018919
16 H	1.962611	-1.244888	-1.809942
17 H	-2.413061	-2.014063	3.215672
18 H	-2.128347	-0.470287	4.062935
19 H	-0.795915	-1.274880	3.189938
20 H	-2.566336	-1.651262	-1.244543
21 H	-4.738352	-1.492887	0.935299
22 H	-3.883640	-2.970211	0.409169
23 H	-4.949708	-2.094830	-0.723221
24 H	-3.938002	0.839351	-0.062719
25 H	-2.637179	0.838914	-1.286540
26 H	4.208456	-1.434190	-0.527767
27 H	4.105084	-0.315668	1.645106
28 H	2.981680	-1.703037	1.722120
29 H	2.343486	-0.068414	1.495785
30 H	4.240495	1.062961	-0.554905
31 H	2.478145	1.093918	-0.786194
32 H	3.533893	0.405714	-2.048708
33 H	1.346287	-3.550311	-1.263166
34 H	3.258741	-4.374813	-2.680019
35 H	4.117989	-2.840969	-2.411202
36 H	2.571203	-2.860386	-3.303665
37 H	4.074470	-3.537494	0.162132
38 H	2.474884	-3.720642	0.942841
39 H	3.055683	-4.940082	-0.212052
40 H	-4.217004	0.139783	-1.668330
41 O	0.516821	-2.736866	1.531593
42 C	-0.319199	-3.685972	1.793030
43 C	0.113431	-4.689785	2.909324
44 C	0.451391	-6.031277	2.207018
45 C	-1.081346	-4.893536	3.873108
46 C	1.337457	-4.183530	3.702609
47 O	-1.433369	-3.850982	1.229703
48 N	-1.946137	-1.110476	0.675680

49 C	-2.243517	-0.270928	1.905060
50 C	-1.537943	1.090750	1.860958
51 C	-1.872531	-1.059600	3.171271
52 C	-3.030450	-1.125051	-0.397741
53 C	-4.222165	-1.974239	0.091939
54 C	-3.469042	0.264053	-0.872867
55 H	-1.900665	-2.108698	0.973754
56 H	0.720686	-6.793296	2.954556
57 H	1.300007	-5.910743	1.519013
58 H	-0.413939	-6.389846	1.633296
59 H	-0.831183	-5.651633	4.630786
60 H	-1.969473	-5.219431	3.318334
61 H	-1.325923	-3.955994	4.393759
62 C	-0.053349	0.296570	-1.303105
63 O	-0.308599	1.460650	-1.149724
64 H	-0.713969	1.726115	-6.150674
65 O	0.367708	-0.149037	-2.686059
66 H	2.331641	2.091922	-5.346356
67 H	1.130929	-1.509098	-5.231258
68 H	2.339751	-0.692082	-4.210311
69 H	2.346368	-0.433339	-5.967976
70 H	-0.620820	-0.010124	-6.519718
71 H	0.676429	1.084321	-7.069787
72 H	2.092219	1.763625	-3.607385
73 C	-0.241989	0.435904	-3.786544
74 O	-1.411992	0.764290	-3.795770
75 C	0.752774	0.638428	-4.943336
76 C	1.579070	1.903195	-4.567865
77 C	1.698651	-0.578278	-5.091425
78 C	-0.028005	0.875992	-6.252598
79 H	0.928196	2.785115	-4.488494

Bisamine palladium anhydride pivalate **Int-13g**



DZP:

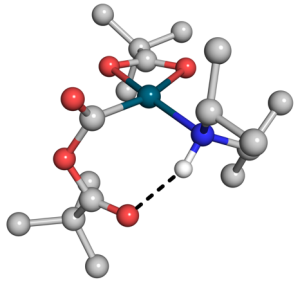
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9685.66	467.046	286.682	-9331.32

Atom	X	Y	Z
1 Pd	0.099661	-0.313772	0.091253
2 H	-1.740460	-6.074222	1.467945
3 H	-0.048502	-5.533787	1.308958
4 H	-2.502725	1.515693	2.750619
5 H	-0.413631	2.390819	3.701761
6 H	-0.443386	2.801625	1.972558
7 H	0.563697	1.456993	2.542362
8 H	-1.263858	-5.015766	0.111068
9 N	1.742464	-1.275494	-0.986473
10 C	2.953896	-1.576306	-0.123409
11 C	3.248501	-0.390659	0.808038
12 C	4.195062	-1.906432	-0.977291
13 C	1.182209	-2.419140	-1.851565
14 C	1.753533	-2.385171	-3.281176
15 C	1.331484	-3.799031	-1.201331
16 H	1.987579	-0.514588	-1.646007
17 H	-2.282183	-0.867903	3.434588
18 H	-1.357259	0.183429	4.528414
19 H	-0.508920	-0.766930	3.284349
20 H	-2.436176	0.796358	-0.817674
21 H	-4.386040	1.125189	1.551364
22 H	-4.241568	-0.310937	0.500649
23 H	-4.812568	1.234926	-0.170503
24 H	-3.148986	3.121955	-0.598534
25 H	-2.728775	3.157820	1.125068
26 H	2.675390	-2.430656	0.503027
27 H	4.140509	-0.616099	1.409124
28 H	2.410509	-0.217443	1.493646
29 H	3.439119	0.530124	0.239128
30 H	5.059498	-2.061426	-0.316126
31 H	4.427554	-1.073044	-1.656885
32 H	4.064379	-2.814213	-1.574099
33 H	0.108596	-2.200325	-1.916476
34 H	2.813282	-2.667317	-3.305791
35 H	1.649618	-1.387152	-3.720490
36 H	1.196297	-3.101981	-3.902058

37 H	2.363546	-4.169379	-1.257327
38 H	1.020503	-3.787971	-0.156186
39 H	0.691120	-4.510237	-1.740421
40 H	-1.454715	2.972480	-0.119001
41 O	0.642302	-2.677707	2.139612
42 C	-0.459690	-2.845776	1.588685
43 C	-1.425194	-3.987061	2.044198
44 C	-2.903867	-3.587014	1.830881
45 C	-1.172561	-4.305388	3.533658
46 C	-1.096614	-5.231079	1.175209
47 O	-0.908345	-2.144948	0.576911
48 N	-1.687810	0.454490	1.104438
49 C	-1.561341	0.990012	2.526094
50 C	-0.394796	1.972984	2.684578
51 C	-1.419203	-0.191299	3.497497
52 C	-2.669363	1.179919	0.184407
53 C	-4.112346	0.780300	0.544104
54 C	-2.476357	2.698406	0.160017
55 H	-2.060737	-0.503520	1.190480
56 H	-3.564430	-4.405254	2.156177
57 H	-3.104517	-3.368982	0.774869
58 H	-3.159704	-2.694163	2.418960
59 H	-1.821465	-5.133307	3.856092
60 H	-1.388917	-3.429380	4.162132
61 H	-0.125478	-4.587570	3.698116
62 C	0.778808	1.486740	-0.399551
63 O	1.415333	2.407546	-0.059178
64 H	-0.801965	3.374269	-4.550631
65 O	-0.205054	1.892986	-1.986648
66 H	-0.259240	0.924821	-6.417749
67 H	-1.976179	0.066962	-3.132502
68 H	-0.742046	-0.940015	-3.931053
69 H	-2.043190	-0.198702	-4.897009
70 H	-2.049706	2.591053	-3.555343
71 H	-2.038185	2.348709	-5.325541
72 H	1.018872	0.149697	-5.441972
73 C	0.396222	1.342659	-3.003032
74 O	1.549552	0.856044	-2.977990
75 C	-0.494758	1.221530	-4.273549
76 C	0.380958	1.037108	-5.530143
77 C	-1.368830	-0.044897	-4.041147

78 C	-1.404497	2.461761	-4.433163
79 H	1.034137	1.908564	-5.680626

Monoamine palladium anhydride pivalate **Int-13h**



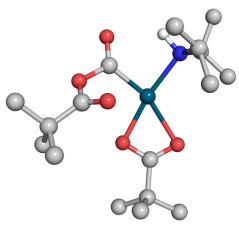
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7065.67	328.884	230.926	-6827.57

Atom	X	Y	Z
1 Pd	1.263144	-1.847988	-0.443043
2 H	0.811971	-4.681528	-5.604967
3 H	2.120946	-3.652890	-4.967207
4 C	0.463795	-0.023566	-0.377593
5 O	0.977407	1.058251	-0.469456
6 H	-3.243151	-0.085835	-1.649722
7 O	-1.014788	-0.085103	-0.439277
8 H	0.437636	-3.074402	-4.921570
9 N	1.703387	-1.700352	1.680331
10 C	1.832036	-3.068361	2.339790
11 C	3.101303	-3.821272	1.922974
12 C	0.561355	-3.886921	2.042969
13 C	2.723836	-0.619839	2.036883
14 C	3.019078	-0.565377	3.545767
15 C	4.002424	-0.693584	1.190984
16 H	0.795189	-1.334215	2.009185
17 H	-0.754219	-5.464914	-2.235953
18 H	1.558635	-6.585103	-4.064826
19 H	1.670106	-6.324862	-2.301047
20 H	-3.277077	-3.179067	-1.399829
21 H	-4.014173	-1.372342	1.863009
22 H	-3.088309	-2.880064	1.689322
23 H	-4.594365	-2.650581	0.761426
24 H	-4.107831	0.309165	-0.141880
25 H	-4.683225	-1.024319	-1.174622
26 H	1.864205	-2.886392	3.425908

27 H	3.166362	-3.907345	0.831378
28 H	3.064153	-4.836348	2.343771
29 H	4.008601	-3.337697	2.299879
30 H	0.569506	-4.796048	2.660362
31 H	0.526988	-4.188794	0.987749
32 H	-0.346307	-3.315904	2.278334
33 H	2.203946	0.307623	1.758959
34 H	3.598441	0.343466	3.761843
35 H	3.611876	-1.427460	3.879124
36 H	2.092123	-0.523297	4.134580
37 H	4.624612	-1.557370	1.448883
38 H	3.757820	-0.744676	0.122129
39 H	4.594888	0.216462	1.363365
40 H	-1.780182	-3.371874	-0.452143
41 O	0.759913	-2.384701	-2.463445
42 C	1.199282	-3.596205	-2.323112
43 C	0.890011	-4.615700	-3.427823
44 C	-0.598139	-5.027252	-3.232266
45 C	1.802846	-5.852103	-3.282454
46 C	1.076134	-3.960643	-4.817557
47 O	1.804166	-3.937466	-1.253096
48 C	-1.646237	-0.850759	0.516756
49 O	-1.193427	-0.998788	1.643616
50 C	-2.909687	-1.526534	-0.022712
51 H	2.860678	-5.572707	-3.384800
52 C	-2.409155	-2.646193	-0.985874
53 C	-3.698774	-2.145649	1.148636
54 C	-3.786925	-0.512119	-0.798129
55 H	-1.817710	-2.228510	-1.808463
56 H	-0.877551	-5.775717	-3.988488
57 H	-1.258116	-4.156831	-3.336868

Monoamine palladium anhydride pivalate **Int-13i**



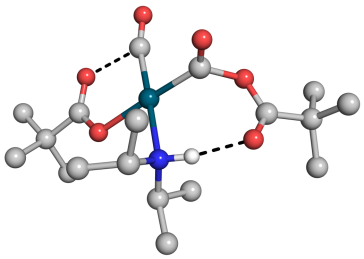
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7066.27	328.792	232.229	-6828.78

Atom	X	Y	Z
1 Pd	1.025989	-2.328230	0.076281
2 H	0.165542	-4.111635	-5.484618
3 H	1.240825	-2.847475	-4.831553
4 C	-0.237034	-0.965491	0.794914
5 O	-0.000262	-0.073566	1.579503
6 H	-4.051580	-0.182473	-0.141770
7 O	-1.549082	-0.988191	0.196418
8 H	-0.471143	-2.892945	-4.347544
9 N	2.036712	-2.265363	1.980811
10 C	1.632321	-3.404592	2.914326
11 C	1.406936	-4.726050	2.160454
12 C	0.365592	-2.989441	3.677164
13 C	3.532318	-2.000855	1.828814
14 C	4.133980	-1.464250	3.141413
15 C	4.296734	-3.213793	1.287838
16 H	1.654765	-1.399724	2.390422
17 H	-0.230712	-6.030569	-2.237737
18 H	1.760494	-5.928564	-4.659929
19 H	2.246448	-5.990906	-2.942054
20 H	-3.682588	-1.525701	-2.994497
21 H	-4.300544	-3.969219	-0.201024
22 H	-3.182013	-4.208405	-1.560021
23 H	-4.785676	-3.482114	-1.849185
24 H	-4.822150	-1.592395	0.636780
25 H	-5.297861	-1.116370	-1.014452
26 H	2.453817	-3.538864	3.633719
27 H	0.507286	-4.656938	1.533066
28 H	1.255161	-5.532466	2.892676
29 H	2.252692	-4.997211	1.520778
30 H	0.084817	-3.782389	4.383796
31 H	-0.470212	-2.841779	2.979459
32 H	0.523437	-2.061898	4.246741
33 H	3.579849	-1.195745	1.079922
34 H	5.173100	-1.153506	2.964161
35 H	4.142016	-2.229464	3.929920
36 H	3.574970	-0.590128	3.504760
37 H	4.331224	-4.027761	2.025049
38 H	3.850721	-3.590341	0.359412
39 H	5.331845	-2.911803	1.075610

40 H	-2.033825	-2.142930	-2.665685
41 O	0.199764	-2.675250	-1.860048
42 C	1.036124	-3.624859	-2.150759
43 C	0.758108	-4.454653	-3.414459
44 C	-0.459924	-5.363288	-3.081070
45 C	1.984418	-5.321024	-3.770903
46 C	0.399417	-3.513625	-4.591660
47 O	2.006752	-3.886351	-1.369425
48 C	-2.209397	-2.214235	0.076136
49 O	-1.908147	-3.185050	0.741670
50 C	-3.366267	-2.121329	-0.927346
51 H	2.858986	-4.692225	-3.989067
52 C	-2.855480	-1.536160	-2.270125
53 C	-3.943979	-3.536278	-1.144923
54 C	-4.451517	-1.189344	-0.316786
55 H	-2.489114	-0.510466	-2.139608
56 H	-0.714939	-5.981053	-3.954612
57 H	-1.331613	-4.753799	-2.813970

Carbonyl palladium anhydride κ² pivalate **Int-13j**



DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7412.72	335.191	241.717	-7172.56

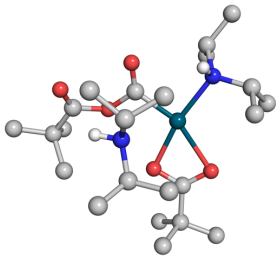
Atom	X	Y	Z
1 Pd	0.283520	-0.086092	0.526957
2 H	-1.419584	-5.527372	-1.307820
3 H	-0.792916	-3.901493	-1.706926
4 H	0.865162	5.519968	-2.259962
5 O	-0.434982	2.768386	-0.041104
6 H	-1.391529	4.476122	-4.067263
7 H	-1.109789	-5.138202	2.451596
8 H	-2.400874	-4.081731	-0.955064
9 N	1.745465	0.000157	-1.144216
10 C	3.166140	-0.338298	-0.726897
11 C	3.312537	-1.811366	-0.326170

12 C	3.615615	0.612403	0.391781
13 C	1.220716	-0.752990	-2.357097
14 C	2.182062	-0.664415	-3.557401
15 C	-0.162345	-0.196284	-2.730670
16 H	1.742340	1.005467	-1.396706
17 H	-2.274140	4.519819	-0.385269
18 H	-2.739209	3.199073	-1.481799
19 H	-2.861261	4.892264	-2.026436
20 H	-0.094553	5.831332	-0.786679
21 H	-0.744226	6.287324	-2.383759
22 H	0.172725	3.634095	-3.878529
23 C	0.079907	3.158383	-1.220961
24 H	1.322785	-4.386617	-0.364107
25 C	0.512708	1.907804	0.859177
26 H	3.805515	-0.141686	-1.602449
27 H	4.351734	-1.998218	-0.021523
28 H	3.075071	-2.490876	-1.153953
29 H	2.647503	-2.057886	0.510754
30 H	4.688910	0.469209	0.578864
31 H	3.074030	0.413886	1.326727
32 H	3.448874	1.662526	0.116589
33 H	1.106399	-1.796601	-2.043789
34 H	3.139135	-1.165180	-3.367500
35 H	2.379556	0.385968	-3.819866
36 H	1.718010	-1.151701	-4.426584
37 H	-0.084664	0.854658	-3.035778
38 H	-0.864085	-0.269062	-1.888963
39 H	-0.578398	-0.771150	-3.569037
40 H	1.217614	-4.861399	1.347854
41 O	0.121600	-2.183779	0.094834
42 C	-0.671616	-2.891611	0.830315
43 C	-0.722691	-4.399701	0.428029
44 C	-1.552292	-5.204679	1.448216
45 C	0.726321	-4.945000	0.367217
46 C	-1.375322	-4.479109	-0.977080
47 O	-1.370659	-2.464603	1.783748
48 O	1.182387	2.802165	-1.643772
49 C	-0.825792	4.142081	-1.991995
50 C	-0.846384	3.722003	-3.482341
51 C	-2.263063	4.187846	-1.430943
52 C	-0.151162	5.535918	-1.843916

53 H	-1.356424	2.756987	-3.611005
54 O	1.152309	2.522601	1.653049
55 H	0.711570	-6.006939	0.080228
56 H	-1.583209	-6.262441	1.148178
57 H	-2.580409	-4.824758	1.507518
58 C	-1.020116	-0.196006	2.020742
59 O	-1.696225	0.090932	2.908367

A1.3E Precarbamoyl formation anhydride geometries

Amine palladium anhydride κ² pivalate with external amine **Int-14b**



DZP:

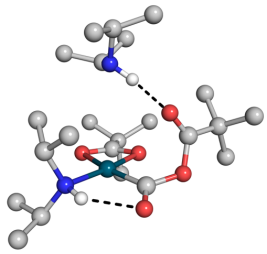
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9672.33	466.564	294.819	-9321.67

Atom	X	Y	Z
1 Pd	0.948682	-1.853786	-0.020178
2 H	-3.444766	-5.747303	0.288714
3 H	-1.735846	-5.821954	-0.215288
4 H	-1.183440	2.686207	1.068969
5 H	0.105631	4.104562	-0.564429
6 H	-1.332957	3.360993	-1.309685
7 H	0.281762	2.679029	-1.627408
8 H	-2.784555	-4.521909	-0.833819
9 N	2.994651	-1.248820	0.536719
10 C	3.359848	-1.624720	1.968068
11 C	3.417817	-3.143774	2.181777
12 C	2.368649	-0.960648	2.936691
13 C	4.043983	-1.519093	-0.547379
14 C	5.461365	-1.090013	-0.130675
15 C	4.008195	-2.957623	-1.084183
16 H	2.886257	-0.224097	0.537829
17 H	0.776440	1.321189	1.887646
18 H	1.252122	2.978564	1.438024
19 H	1.593220	1.611686	0.334830
20 H	-2.293143	-0.693724	0.234283
21 H	-1.458625	0.941653	2.694602
22 H	-0.787932	-0.628654	2.170741
23 H	-2.481231	-0.506937	2.700316
24 H	-4.245818	0.527199	1.184645
25 H	-3.344770	2.060997	1.145850
26 H	4.355264	-1.198876	2.168164
27 H	3.586531	-3.344408	3.249326
28 H	4.237378	-3.605931	1.622551

29 H	2.471202	-3.615434	1.891253
30 H	2.702555	-1.135332	3.969156
31 H	1.363005	-1.383723	2.824795
32 H	2.319771	0.123897	2.777509
33 H	3.721647	-0.856736	-1.359517
34 H	6.114076	-1.121465	-1.014420
35 H	5.891048	-1.759792	0.626514
36 H	5.471936	-0.061526	0.259420
37 H	4.459819	-3.676946	-0.391740
38 H	2.975079	-3.269668	-1.286109
39 H	4.572358	-2.996551	-2.026817
40 H	-3.766964	1.238375	-0.376417
41 O	0.067737	-3.315341	1.620256
42 C	-0.961630	-3.390435	0.874693
43 C	-2.180311	-4.252559	1.257037
44 C	-3.357733	-3.295297	1.586619
45 C	-1.853096	-5.128012	2.484911
46 C	-2.560008	-5.141282	0.043730
47 O	-1.023803	-2.729093	-0.233788
48 N	-1.026329	0.892774	-0.091612
49 C	-0.491110	2.212477	0.349709
50 C	-0.350421	3.149629	-0.861957
51 C	0.868713	2.020793	1.052031
52 C	-2.121042	0.281401	0.708575
53 C	-1.679360	0.008327	2.155317
54 C	-3.446828	1.077320	0.663394
55 H	-1.360944	0.990269	-1.052232
56 H	-4.255579	-3.881497	1.833278
57 H	-3.585033	-2.646969	0.730580
58 H	-3.113281	-2.659932	2.448008
59 H	-2.731788	-5.730873	2.757336
60 H	-1.570445	-4.507000	3.344817
61 H	-1.015576	-5.805594	2.270152
62 C	0.982006	-0.645441	-1.595443
63 O	1.720569	0.273855	-1.859960
64 H	-1.935706	0.108821	-5.783587
65 O	-0.056628	-1.100619	-2.456498
66 H	-2.363189	-2.846365	-4.950978
67 H	-3.301387	-0.316287	-2.267909
68 H	-2.491883	-1.872588	-1.940615
69 H	-3.846704	-1.786214	-3.108516

70 H	-2.969478	0.847748	-4.541547
71 H	-3.507474	-0.633097	-5.379951
72 H	-1.068263	-2.986248	-3.731335
73 C	-0.781218	-0.227395	-3.282909
74 O	-0.548020	0.954359	-3.408166
75 C	-1.972076	-0.990606	-3.888065
76 C	-1.501168	-2.334671	-4.499152
77 C	-2.963255	-1.260570	-2.717342
78 C	-2.636026	-0.108192	-4.965254
79 H	-0.749902	-2.166243	-5.283629

Amine palladium anhydride κ² pivalate with external amine **Int-14c**



DZP:

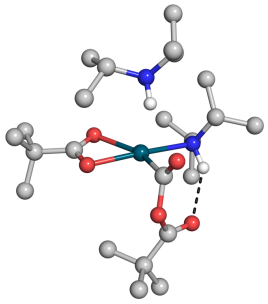
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9675.62	467.446	296.601	-9324.78

Atom	X	Y	Z
1 Pd	1.310052	-2.269950	-0.714889
2 H	-3.176055	-5.861863	0.047787
3 H	-1.445041	-5.838614	0.483301
4 H	-1.284397	2.562951	1.522870
5 H	-1.425769	4.061253	-0.502093
6 H	-2.483027	2.639147	-0.687253
7 H	-0.914043	2.693250	-1.525985
8 H	-1.952207	-5.441697	-1.182488
9 N	3.291223	-1.951404	0.061980
10 C	3.420380	-0.706742	0.934719
11 C	2.213080	-0.509791	1.863596
12 C	3.602562	0.505106	0.008270
13 C	3.896956	-3.244736	0.602903
14 C	5.431800	-3.143814	0.683800
15 C	3.274821	-3.691555	1.930518
16 H	3.819798	-1.757862	-0.801480
17 H	1.190038	2.373969	1.625390
18 H	0.726672	3.913533	0.838625

19 H	1.292522	2.532680	-0.140403
20 H	-1.630084	-0.984240	0.849844
21 H	-1.544166	1.024422	3.166325
22 H	-0.485410	-0.391041	2.930667
23 H	-2.225359	-0.612587	3.255320
24 H	-3.927483	-0.234570	1.412267
25 H	-3.433033	1.468820	1.313300
26 H	4.331169	-0.834985	1.539785
27 H	2.449874	0.288092	2.583345
28 H	1.962620	-1.412881	2.428731
29 H	1.325206	-0.191015	1.299482
30 H	3.678849	1.422734	0.605534
31 H	2.734572	0.606147	-0.657807
32 H	4.511686	0.411699	-0.604176
33 H	3.647043	-3.989324	-0.167869
34 H	5.847186	-4.133040	0.921861
35 H	5.753332	-2.446992	1.469761
36 H	5.859970	-2.816878	-0.274447
37 H	3.556840	-3.017422	2.750574
38 H	2.181352	-3.740653	1.868128
39 H	3.653305	-4.693639	2.176374
40 H	-3.425417	0.455773	-0.151404
41 O	-0.073062	-3.201570	0.903378
42 C	-0.980425	-3.213262	0.010170
43 C	-2.355060	-3.847715	0.278103
44 C	-3.447204	-3.173814	-0.583225
45 C	-2.707983	-3.734154	1.778963
46 C	-2.219380	-5.346177	-0.120954
47 O	-0.736279	-2.733916	-1.171372
48 N	-0.709835	0.810277	0.519237
49 C	-0.737926	2.291691	0.606203
50 C	-1.439144	2.964095	-0.597876
51 C	0.706525	2.816492	0.744973
52 C	-1.761022	0.040361	1.218107
53 C	-1.485685	0.013139	2.735367
54 C	-3.223945	0.459875	0.927739
55 H	-0.652643	0.528274	-0.460687
56 H	-4.413228	-3.669474	-0.406420
57 H	-3.208269	-3.240681	-1.651347
58 H	-3.555657	-2.113850	-0.322685
59 H	-3.662061	-4.245835	1.972639

60 H	-2.812817	-2.684086	2.079829
61 H	-1.927301	-4.188997	2.400955
62 C	2.018664	-1.722996	-2.499433
63 O	3.157970	-1.728165	-2.904617
64 H	-0.463140	0.126095	-5.780494
65 O	0.954542	-1.480392	-3.464582
66 H	-2.541046	-2.072505	-4.841058
67 H	-2.231735	0.855971	-2.523095
68 H	-2.358252	-0.834755	-1.984774
69 H	-3.368216	-0.254600	-3.336554
70 H	-1.050877	1.423407	-4.702774
71 H	-2.215923	0.389665	-5.576848
72 H	-1.515901	-2.740054	-3.537286
73 C	0.063500	-0.472300	-3.144530
74 O	0.364202	0.432326	-2.383469
75 C	-1.283378	-0.595804	-3.869217
76 C	-1.546639	-2.031849	-4.373731
77 C	-2.381100	-0.175477	-2.858891
78 C	-1.245955	0.403324	-5.060142
79 H	-0.801225	-2.337525	-5.119414

Amine palladium anhydride κ² pivalate with external amine **Int-14d**



DZP:

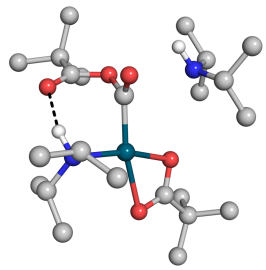
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9672.42	465.708	289.099	-9320.37

Atom	X	Y	Z
1 Pd	1.254422	-1.939219	-0.415006
2 H	1.156795	-4.318893	-5.775688
3 H	2.394591	-3.445769	-4.832359
4 H	4.908621	-0.001008	-3.499582
5 H	2.972369	-0.781167	-4.877669
6 H	2.585357	0.706077	-3.969675
7 H	1.969941	-0.877903	-3.418297
8 H	0.751113	-2.781503	-4.956751

9 N	1.850453	-1.641184	1.661886
10 C	2.057965	-2.927050	2.461225
11 C	2.839866	-4.001972	1.689967
12 C	0.687042	-3.455590	2.908770
13 C	2.889288	-0.543257	1.886547
14 C	2.736059	0.069330	3.291427
15 C	4.314585	-1.013845	1.592936
16 H	0.961283	-1.249034	2.005054
17 H	5.429157	-2.132121	-2.330879
18 H	4.688157	-2.457370	-3.922905
19 H	3.726012	-2.622600	-2.425294
20 H	4.466473	1.327385	-0.174917
21 H	6.324813	-0.314596	-0.526233
22 H	6.885628	1.374201	-0.675038
23 H	6.648591	0.384397	-2.129396
24 H	5.298063	3.178507	-1.629436
25 H	4.966681	2.208432	-3.083375
26 H	2.632072	-2.647110	3.357229
27 H	2.222632	-4.452687	0.905007
28 H	3.137073	-4.793301	2.393757
29 H	3.744338	-3.605700	1.218288
30 H	0.815815	-4.387369	3.476841
31 H	0.054360	-3.666935	2.035045
32 H	0.160172	-2.729253	3.542229
33 H	2.633271	0.229303	1.150781
34 H	3.404682	0.936872	3.385460
35 H	3.000757	-0.645459	4.082923
36 H	1.706270	0.415867	3.461125
37 H	4.649266	-1.784604	2.300484
38 H	4.385638	-1.380170	0.562089
39 H	4.994511	-0.156836	1.689818
40 H	3.619738	2.731167	-2.040042
41 O	0.572497	-2.457609	-2.372395
42 C	1.133518	-3.627079	-2.379152
43 C	0.911501	-4.510740	-3.615303
44 C	-0.604282	-4.846631	-3.679224
45 C	1.744616	-5.803812	-3.501002
46 C	1.329278	-3.709969	-4.875812
47 O	1.826878	-4.009668	-1.386262
48 N	3.884268	-0.011460	-1.632454
49 C	4.088841	-0.551624	-3.008653

50 C	2.827106	-0.362569	-3.870847
51 C	4.507469	-2.034026	-2.922068
52 C	4.788509	1.083404	-1.201561
53 C	6.249140	0.600078	-1.127661
54 C	4.661514	2.379037	-2.040392
55 H	2.925119	0.332887	-1.544760
56 H	-0.811262	-5.470000	-4.561796
57 H	-1.200928	-3.928262	-3.745394
58 H	-0.919295	-5.400117	-2.782824
59 H	1.575826	-6.432639	-4.387434
60 H	1.465100	-6.374597	-2.605955
61 H	2.816122	-5.572731	-3.432996
62 C	0.420096	-0.130007	-0.392424
63 O	0.952385	0.941621	-0.552125
64 H	-3.276416	-0.082539	-1.589822
65 O	-1.030730	-0.167999	-0.427658
66 H	-3.400048	-3.172904	-1.403059
67 H	-4.030868	-1.413629	1.904822
68 H	-3.140062	-2.937802	1.698154
69 H	-4.654904	-2.663174	0.794309
70 H	-4.094525	0.311848	-0.055727
71 H	-4.736313	-0.981474	-1.100210
72 H	-1.889970	-3.432059	-0.489602
73 C	-1.668182	-0.938836	0.536599
74 O	-1.199188	-1.101159	1.650150
75 C	-2.956425	-1.565957	0.002244
76 C	-2.507630	-2.676930	-0.995053
77 C	-3.742962	-2.184033	1.175875
78 C	-3.815447	-0.506677	-0.734242
79 H	-1.916740	-2.260306	-1.817855

Amine palladium anhydride κ^2 pivalate with external amine **Int-14e**



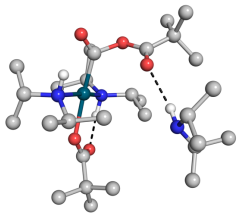
DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9668.63	466.343	296.081	-9318.69

Atom	X	Y	Z
1 Pd	1.142282	-2.172379	-0.483946
2 H	2.135164	-5.465596	-5.226589
3 H	3.059074	-4.216364	-4.350875
4 H	-1.677784	-0.394854	-5.001540
5 H	-3.978663	-0.665690	-4.001139
6 H	-3.211387	0.867037	-3.507781
7 H	-3.260478	-0.512880	-2.378931
8 H	1.367160	-3.907743	-4.810840
9 N	1.756205	-1.585175	1.531956
10 C	2.097264	-2.782455	2.409254
11 C	3.423769	-3.456515	2.035416
12 C	0.923124	-3.778276	2.367510
13 C	2.684944	-0.374951	1.568705
14 C	3.129964	-0.015988	2.997356
15 C	3.864292	-0.486239	0.590957
16 H	0.849160	-1.242496	1.893903
17 H	-0.805000	-2.661545	-4.331138
18 H	-2.575549	-2.685394	-4.571546
19 H	-1.858891	-2.651905	-2.924672
20 H	1.176289	0.638298	-2.937107
21 H	1.429100	-1.621747	-3.947783
22 H	2.210788	-0.356905	-4.943524
23 H	0.660596	-1.056463	-5.452639
24 H	1.201704	2.011873	-5.022301
25 H	-0.396083	1.382072	-5.483779
26 H	2.171913	-2.399010	3.439952
27 H	3.436894	-3.736047	0.975777
28 H	3.534735	-4.372424	2.633619
29 H	4.285187	-2.814764	2.249626
30 H	1.080809	-4.552112	3.131790
31 H	0.862485	-4.269146	1.386562
32 H	-0.031450	-3.276495	2.574170
33 H	2.042121	0.437443	1.205120
34 H	3.630536	0.962362	2.978235
35 H	3.839583	-0.747585	3.406521
36 H	2.268360	0.058410	3.676038
37 H	4.587206	-1.254100	0.887585
38 H	3.503570	-0.721013	-0.419000
39 H	4.387982	0.479743	0.553370
40 H	-0.224904	2.389032	-4.021753

41 O	0.723775	-3.164749	-2.343651
42 C	1.500997	-4.161119	-2.080739
43 C	1.588097	-5.290440	-3.119066
44 C	0.164564	-5.885150	-3.295244
45 C	2.572286	-6.379552	-2.645671
46 C	2.066610	-4.677244	-4.462313
47 O	2.157299	-4.189127	-0.986042
48 N	-0.700097	-0.186301	-3.107046
49 C	-1.790748	-0.741155	-3.957726
50 C	-3.144929	-0.229024	-3.433194
51 C	-1.758434	-2.281950	-3.952947
52 C	0.519526	0.342919	-3.772616
53 C	1.248784	-0.744469	-4.576810
54 C	0.256810	1.607005	-4.627277
55 H	-1.085043	0.572623	-2.537879
56 H	0.182341	-6.670509	-4.065784
57 H	-0.544067	-5.104080	-3.598071
58 H	-0.190823	-6.331877	-2.355127
59 H	2.621280	-7.185109	-3.393384
60 H	2.251502	-6.808220	-1.687073
61 H	3.580402	-5.965593	-2.509074
62 C	0.015584	-0.541546	-0.478051
63 O	0.290797	0.625629	-0.458340
64 H	-4.013312	-0.083654	-0.361606
65 O	-1.473194	-0.901571	-0.290830
66 H	-4.555849	-3.158376	0.238265
67 H	-3.441090	-1.157481	3.233678
68 H	-2.973372	-2.829357	2.857020
69 H	-4.663353	-2.307741	2.625715
70 H	-4.075505	0.463289	1.332875
71 H	-5.277512	-0.707732	0.730031
72 H	-2.837923	-3.611228	0.386471
73 C	-1.843384	-1.119628	0.990109
74 O	-1.100694	-0.975461	1.961740
75 C	-3.311577	-1.583112	1.087474
76 C	-3.525185	-2.789993	0.136086
77 C	-3.613571	-1.993498	2.543856
78 C	-4.224333	-0.398981	0.666954
79 H	-3.351753	-2.507627	-0.908279

Bisamine palladium anhydride pivalate with external amine **Int-14f**



DZP:

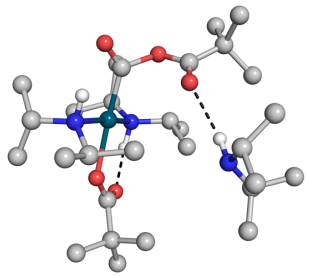
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-12295.17	603.636	348.723	-11828.63

Atom	X	Y	Z
1 Pd	-0.258188	-1.163321	0.643230
2 H	3.378642	-3.324953	-3.576674
3 H	1.854099	-4.130037	-3.119295
4 H	-3.869206	-0.663160	-1.198234
5 H	-3.300112	-0.826810	1.816912
6 H	-4.889009	-0.837686	1.017719
7 H	-3.887385	0.632504	0.996240
8 H	2.788440	-3.246184	-1.893403
9 N	1.332566	-2.242479	1.771164
10 C	1.014992	-3.715346	1.995230
11 C	1.068949	-4.524005	0.693504
12 C	-0.339521	-3.867149	2.703123
13 C	2.716095	-1.960952	1.208566
14 C	3.831945	-2.659626	2.009344
15 C	2.933928	-0.445882	1.161919
16 H	1.296327	-1.804719	2.704537
17 H	-2.612232	-2.830507	-1.312910
18 H	-4.119282	-2.943070	-0.357960
19 H	-2.542318	-2.866280	0.465481
20 H	-2.100175	1.624676	0.033344
21 H	-3.869129	1.388672	-1.700603
22 H	-2.638914	0.948610	-2.919725
23 H	-2.686622	2.594362	-2.238790
24 H	-0.097763	0.992433	-2.212027
25 H	-0.345290	2.593139	-1.475529
26 H	1.786624	-4.099506	2.682143
27 H	0.845615	-5.576067	0.921180
28 H	2.056973	-4.483130	0.219685
29 H	0.337268	-4.149206	-0.031655
30 H	-0.488322	-4.922485	2.971316

31 H	-1.162061	-3.558027	2.046417
32 H	-0.389723	-3.260215	3.615033
33 H	2.697282	-2.342271	0.182127
34 H	3.772302	-3.753584	1.954966
35 H	3.800014	-2.358228	3.067921
36 H	4.807074	-2.359551	1.601158
37 H	2.832063	0.003574	2.160301
38 H	2.217904	0.050602	0.503213
39 H	3.936939	-0.217975	0.779382
40 H	0.318006	1.264257	-0.504492
41 O	0.710386	-2.010998	-1.117260
42 C	0.454165	-1.819658	-2.368109
43 C	1.707104	-1.945962	-3.286766
44 C	2.595555	-0.708214	-2.980960
45 C	1.298827	-1.949756	-4.773300
46 C	2.480910	-3.242607	-2.945326
47 O	-0.664492	-1.503399	-2.852771
48 N	-1.863324	-0.365347	-0.617606
49 C	-3.225692	-0.964437	-0.356110
50 C	-3.858440	-0.462212	0.945368
51 C	-3.114968	-2.497417	-0.395051
52 C	-1.829930	1.120108	-0.897844
53 C	-2.824301	1.529503	-2.003762
54 C	-0.398432	1.513126	-1.293976
55 H	-1.519532	-0.824488	-1.500407
56 H	3.518592	-0.744888	-3.578904
57 H	2.862496	-0.671918	-1.917401
58 H	2.068619	0.224754	-3.226975
59 H	2.195037	-2.010754	-5.408789
60 H	0.745697	-1.036842	-5.028969
61 H	0.651359	-2.808844	-4.999988
62 C	-0.780839	-0.311596	2.364941
63 O	-0.675971	-0.714077	3.492916
64 H	-3.021460	2.900958	3.156305
65 O	-1.393554	1.108633	2.277924
66 H	-0.937823	5.154271	3.704429
67 H	-1.054595	3.975594	0.123950
68 H	0.471952	4.303956	0.971968
69 H	-0.920797	5.396309	1.185567
70 H	-3.070673	3.065300	1.387928
71 H	-3.028484	4.520658	2.407997

72 H	-0.883626	3.538553	4.458243
73 C	-0.483388	2.102608	2.177233
74 O	0.723406	1.914265	2.057711
75 C	-1.109375	3.515024	2.270313
76 C	-0.559296	4.129022	3.589294
77 C	-0.617967	4.346977	1.059968
78 C	-2.652244	3.492243	2.309115
79 H	0.537204	4.153955	3.575047
80 H	1.987566	2.546060	0.323179
81 N	2.922367	2.627605	-0.080487
82 C	3.832466	3.032213	1.018942
83 C	3.422375	4.302338	1.811978
84 C	5.304706	3.106241	0.580019
85 C	2.836175	3.323603	-1.386238
86 C	3.933359	2.855452	-2.371087
87 C	2.738325	4.870708	-1.364982
88 H	3.752908	2.197012	1.734729
89 H	3.548202	5.220775	1.224686
90 H	4.037422	4.393320	2.722298
91 H	2.373368	4.223014	2.121931
92 H	5.594429	2.199926	0.031584
93 H	5.952033	3.205270	1.463855
94 H	5.489998	3.975734	-0.065704
95 H	1.886688	2.954979	-1.802950
96 H	4.018165	1.762036	-2.338523
97 H	4.913452	3.289312	-2.134926
98 H	3.673519	3.158676	-3.397210
99 H	2.525842	5.251393	-2.376751
100 H	3.679544	5.326374	-1.028369
101 H	1.934168	5.204983	-0.695825

Bisamine palladium anhydride pivalate with external amine **Int-14g**



DZP:

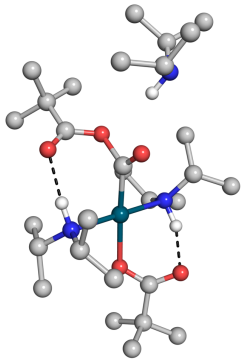
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-12293.09	604.545	354.558	-11827.94

Atom	X	Y	Z
1 Pd	0.114344	-0.663450	0.516466
2 H	1.341753	-5.033403	-4.137518
3 H	-0.242013	-4.248322	-3.860520
4 H	-2.577020	1.249539	0.027717
5 H	-2.820306	-1.684096	-0.831635
6 H	-4.173371	-0.784895	-0.089170
7 H	-2.691652	-1.023707	0.833726
8 H	0.589047	-5.078323	-2.521637
9 N	1.249579	-1.880199	1.967275
10 C	0.566868	-3.201174	2.288864
11 C	0.576853	-4.169006	1.099421
12 C	-0.861551	-2.933570	2.787431
13 C	2.718251	-1.962642	1.594084
14 C	3.536462	-2.800811	2.594303
15 C	3.275164	-0.534281	1.489245
16 H	1.189159	-1.317910	2.830512
17 H	-3.042396	1.885692	-2.365710
18 H	-4.416842	1.051516	-1.626173
19 H	-3.355301	0.168154	-2.749115
20 H	-0.993393	2.347202	-1.549192
21 H	-1.378684	1.047037	-3.717285
22 H	0.228408	0.324529	-3.532219
23 H	0.068626	2.076211	-3.819469
24 H	1.679099	0.840678	-1.510810
25 H	1.459099	2.580301	-1.821757
26 H	1.131578	-3.653852	3.120069
27 H	0.120615	-5.118557	1.412346
28 H	1.591487	-4.380155	0.742918
29 H	0.002160	-3.761083	0.260083
30 H	-1.293872	-3.866511	3.175861
31 H	-1.496414	-2.573799	1.968291
32 H	-0.879054	-2.180088	3.585414
33 H	2.749769	-2.425221	0.600658
34 H	3.239911	-3.856837	2.600075
35 H	3.432179	-2.401018	3.614622
36 H	4.599420	-2.755834	2.318796
37 H	3.187104	-0.004865	2.450230
38 H	2.736650	0.046015	0.731308
39 H	4.337133	-0.568197	1.210284

40 H	1.083812	1.914518	-0.219096
41 O	1.096442	-1.856300	-1.037197
42 C	0.536043	-2.314607	-2.106952
43 C	1.462389	-3.137996	-3.054917
44 C	2.825433	-3.444348	-2.400177
45 C	1.670440	-2.282591	-4.332779
46 C	0.739876	-4.457755	-3.417943
47 O	-0.660769	-2.125449	-2.448057
48 N	-1.059776	0.293997	-1.064326
49 C	-2.530875	0.475259	-0.742330
50 C	-3.081133	-0.843888	-0.172054
51 C	-3.374510	0.925659	-1.952116
52 C	-0.393328	1.458367	-1.782427
53 C	-0.377863	1.212160	-3.306145
54 C	1.042917	1.709566	-1.292744
55 H	-1.006107	-0.541858	-1.692115
56 H	3.458288	-4.013758	-3.098567
57 H	2.694543	-4.040799	-1.487017
58 H	3.347864	-2.519370	-2.124575
59 H	2.284442	-2.831033	-5.063235
60 H	2.185557	-1.340762	-4.091012
61 H	0.702799	-2.041876	-4.792563
62 C	-0.380334	0.540693	2.027760
63 O	-0.249896	0.384804	3.215960
64 H	-1.032313	4.499142	3.943230
65 O	-0.944961	1.894078	1.607070
66 H	-0.589143	6.422256	1.529735
67 H	-2.726783	3.432613	0.705461
68 H	-1.487039	4.103547	-0.375103
69 H	-2.555285	5.193862	0.539216
70 H	-2.408554	3.584685	3.279329
71 H	-2.349270	5.355020	3.095045
72 H	0.709632	5.533229	2.374571
73 C	-0.168655	2.991662	1.858175
74 O	1.014918	2.933006	2.148626
75 C	-0.988264	4.296574	1.753116
76 C	-0.020055	5.482799	1.556832
77 C	-2.002594	4.244640	0.584348
78 C	-1.742653	4.438533	3.106451
79 H	0.533642	5.382900	0.612488
80 H	-2.982565	1.635288	2.330440

81 N	-3.712137	0.957084	2.548706
82 C	-4.979611	1.403135	1.929216
83 C	-5.481005	2.821043	2.321202
84 C	-6.104032	0.362568	2.069442
85 C	-3.564981	0.552515	3.969559
86 C	-3.914660	-0.938503	4.178980
87 C	-4.255342	1.440604	5.033175
88 H	-4.738875	1.459755	0.853425
89 H	-5.890198	2.848430	3.338818
90 H	-6.274440	3.143467	1.627341
91 H	-4.663070	3.552060	2.261080
92 H	-5.751083	-0.633133	1.771013
93 H	-6.954733	0.642076	1.431097
94 H	-6.468928	0.303985	3.103801
95 H	-2.481410	0.639374	4.138303
96 H	-3.435361	-1.545380	3.401173
97 H	-4.997134	-1.118339	4.141414
98 H	-3.552187	-1.278071	5.161327
99 H	-3.946554	1.126934	6.043033
100 H	-5.349631	1.359206	4.979040
101 H	-3.980767	2.496141	4.903613

Bisamine palladium anhydride pivalate with external amine **Int-14h**



DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-12288.75	605.598	358.327	-11824.03

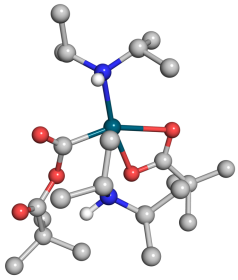
Atom	X	Y	Z
1 Pd	-0.503766	-2.522862	1.490320
2 H	-3.838177	-7.547989	1.842218
3 H	-4.195804	-5.953969	1.130030
4 H	0.307972	-1.431644	-1.202590
5 H	-2.095305	0.324407	-1.927096
6 H	-0.355273	0.709905	-2.015677

7 H	-1.136933	0.534415	-0.443320
8 H	-3.210371	-6.060888	2.605662
9 N	0.381298	-2.879293	3.494356
10 C	-0.574851	-3.339067	4.593214
11 C	-0.852908	-4.846900	4.582611
12 C	-1.877830	-2.529823	4.510574
13 C	1.716376	-3.611170	3.487656
14 C	2.859127	-2.605765	3.284805
15 C	1.752412	-4.726350	2.431557
16 H	0.581897	-1.897055	3.744871
17 H	-1.851584	-1.806684	-3.346317
18 H	-0.123837	-1.456208	-3.558943
19 H	-0.632507	-3.025600	-2.890877
20 H	-3.174157	-2.949802	0.410721
21 H	-2.720834	-0.675270	1.438232
22 H	-4.410103	-0.989956	0.971309
23 H	-3.398798	0.080537	-0.018275
24 H	-3.722026	-1.371028	-2.165140
25 H	-4.863412	-2.354354	-1.226695
26 H	-0.064613	-3.079575	5.539960
27 H	-1.539209	-5.082765	5.408837
28 H	0.057059	-5.442217	4.730046
29 H	-1.320629	-5.131874	3.637735
30 H	-2.438977	-2.795826	3.604479
31 H	-1.674369	-1.453941	4.505308
32 H	-2.504393	-2.756448	5.385405
33 H	1.831471	-4.060514	4.487967
34 H	2.833665	-1.813269	4.046791
35 H	2.799564	-2.136205	2.295499
36 H	3.823373	-3.127648	3.360785
37 H	0.882093	-5.384222	2.498905
38 H	2.664255	-5.328266	2.560185
39 H	1.762416	-4.292221	1.421172
40 H	-3.498688	-3.140504	-2.056565
41 O	-1.537457	-4.456722	1.539151
42 C	-1.560499	-5.240416	0.505602
43 C	-2.149656	-6.660508	0.779752
44 C	-1.067382	-7.475112	1.539404
45 C	-2.482044	-7.363000	-0.553775
46 C	-3.426214	-6.546402	1.646928
47 O	-1.146100	-4.947589	-0.644810

48 N	-1.472584	-2.187983	-0.450069
49 C	-0.747385	-1.344752	-1.491160
50 C	-1.116309	0.142307	-1.464509
51 C	-0.858516	-1.950110	-2.906332
52 C	-2.971180	-2.072994	-0.220418
53 C	-3.392278	-0.832346	0.586648
54 C	-3.804967	-2.242838	-1.504559
55 H	-1.312847	-3.185764	-0.725993
56 H	-1.423636	-8.501782	1.713767
57 H	-0.841730	-7.019980	2.511215
58 H	-0.137153	-7.527409	0.955313
59 H	-2.888632	-8.366283	-0.357497
60 H	-1.586027	-7.459153	-1.179661
61 H	-3.227284	-6.788713	-1.122180
62 C	0.486733	-0.812966	1.373642
63 O	1.532818	-0.516326	0.886927
64 H	-2.721343	1.746093	2.017223
65 O	-0.371782	0.467745	1.848378
66 H	-2.728561	2.304162	5.086597
67 H	0.475616	3.337138	3.346990
68 H	0.367552	2.603304	4.964936
69 H	-0.790190	3.876475	4.478676
70 H	-1.380569	2.823079	1.585903
71 H	-2.605605	3.362996	2.758505
72 H	-2.843817	0.689755	4.345144
73 C	-0.331480	0.717969	3.158717
74 O	0.328736	0.061349	3.970779
75 C	-1.195666	1.928479	3.582503
76 C	-2.142374	1.452065	4.714481
77 C	-0.219649	3.004832	4.128542
78 C	-2.024120	2.497523	2.410023
79 H	-1.568365	1.024546	5.546213
80 H	0.855397	1.646435	0.078437
81 N	1.367349	2.283691	-0.532859
82 C	2.758490	2.346853	-0.008227
83 C	2.878536	2.614791	1.515025
84 C	3.667646	3.280700	-0.823182
85 C	0.518742	3.479672	-0.770818
86 C	0.736046	4.062373	-2.186482
87 C	0.549955	4.608507	0.291292
88 H	3.133900	1.321039	-0.161475

89 H	2.628592	3.650776	1.777060
90 H	3.909073	2.419286	1.853718
91 H	2.210942	1.939428	2.066806
92 H	4.712660	3.147719	-0.507691
93 H	3.407855	4.337210	-0.673541
94 H	3.595415	3.054381	-1.895630
95 H	-0.505254	3.068371	-0.763360
96 H	0.721483	3.253158	-2.929235
97 H	1.696609	4.587400	-2.268044
98 H	-0.060564	4.782176	-2.429636
99 H	1.518530	5.126027	0.300474
100 H	0.364792	4.212041	1.295401
101 H	-0.228227	5.356079	0.070606

Amine palladium anhydride κ^2 acetate with external amine **Int-14i**



DZP:

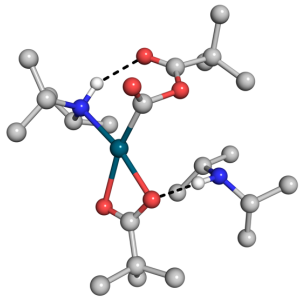
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9672.46	465.802	287.355	-9319.63

Atom	X	Y	Z
1 Pd	0.817131	-1.095026	-0.064550
2 H	-1.568044	-6.473362	0.168466
3 H	0.099980	-5.841279	0.158709
4 H	-2.683281	2.294026	1.323395
5 H	-1.915506	4.166097	-0.181042
6 H	-3.068822	3.074317	-0.992555
7 H	-1.328002	2.950230	-1.350831
8 H	-1.084603	-5.241302	-1.033326
9 N	2.509123	0.145463	0.624878
10 C	3.019900	-0.277608	1.998121
11 C	3.610238	-1.695054	1.995597
12 C	1.886785	-0.141999	3.028728
13 C	3.559426	0.466424	-0.442573
14 C	4.697886	1.356123	0.086817
15 C	4.086378	-0.777464	-1.171546

16 H	2.020241	1.039325	0.777851
17 H	-0.368747	1.542140	2.042488
18 H	-0.478358	3.301335	1.775706
19 H	0.279200	2.249915	0.543993
20 H	-2.688919	-1.185504	0.220380
21 H	-2.359899	0.412941	2.820386
22 H	-1.221997	-0.794400	2.160999
23 H	-2.847076	-1.286914	2.687015
24 H	-4.899112	-0.716712	1.269497
25 H	-4.521244	1.018487	1.362150
26 H	3.810915	0.434638	2.279951
27 H	3.878754	-1.968030	3.026380
28 H	4.516166	-1.761184	1.385555
29 H	2.875206	-2.424247	1.630940
30 H	2.288814	-0.343052	4.031671
31 H	1.082876	-0.861131	2.832988
32 H	1.468259	0.873274	3.031416
33 H	2.987174	1.055698	-1.168201
34 H	5.290362	1.717335	-0.765565
35 H	5.375037	0.807257	0.755395
36 H	4.307647	2.233797	0.622182
37 H	4.803853	-1.345448	-0.568030
38 H	3.259170	-1.443776	-1.448958
39 H	4.597586	-0.458195	-2.091025
40 H	-4.703904	0.231354	-0.225378
41 O	0.432083	-2.871502	1.483655
42 C	-0.502999	-3.226756	0.697064
43 C	-1.389404	-4.453249	0.991228
44 C	-2.875558	-4.092358	0.742646
45 C	-1.191102	-4.917606	2.448802
46 C	-0.955627	-5.573738	0.005264
47 O	-0.726193	-2.579928	-0.399703
48 N	-1.984059	0.736021	0.032618
49 C	-1.885482	2.119145	0.579257
50 C	-2.061070	3.142868	-0.555597
51 C	-0.528036	2.316058	1.286157
52 C	-2.814972	-0.248240	0.776157
53 C	-2.273451	-0.488274	2.195600
54 C	-4.323907	0.094961	0.797491
55 H	-2.344727	0.792504	-0.922245
56 H	-3.507640	-4.974642	0.923661

57 H	-3.030702	-3.755776	-0.288838
58 H	-3.203003	-3.291557	1.419393
59 H	-1.820950	-5.797146	2.648681
60 H	-1.468348	-4.120176	3.152210
61 H	-0.142652	-5.183088	2.636262
62 C	0.433889	0.122868	-1.584145
63 O	0.775784	1.264493	-1.780187
64 H	-3.787695	-0.857774	-2.312034
65 O	-0.355835	-0.634981	-2.495012
66 H	-3.774322	-1.342854	-5.401895
67 H	-0.826792	-2.811381	-3.576365
68 H	-0.674404	-1.986884	-5.151511
69 H	-2.041808	-3.088678	-4.852757
70 H	-2.550386	-2.077001	-1.889189
71 H	-3.826121	-2.462355	-3.082515
72 H	-2.476306	-0.190125	-5.811128
73 C	-1.386613	-0.053505	-3.249342
74 O	-1.613613	1.134836	-3.301335
75 C	-2.252457	-1.167460	-3.863017
76 C	-3.110261	-0.567042	-4.996163
77 C	-1.386523	-2.337019	-4.390478
78 C	-3.161872	-1.672465	-2.702190
79 H	-3.723416	0.265054	-4.627770

Amine palladium anhydride κ^2 pivalate with external amine **Int-14j**



DZP:

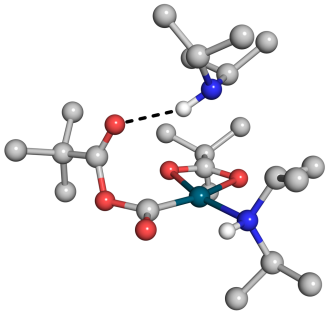
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9669.08	467.508	298.245	-9318.83

Atom	X	Y	Z
1 Pd	1.245601	-1.493200	1.379274
2 H	0.757903	-6.067820	4.941766
3 H	0.455953	-5.722981	3.214091
4 H	4.673917	-0.805127	1.335045
5 H	6.001222	-3.320238	2.495696

6 H	5.697796	-2.938450	0.785874
7 H	4.331657	-3.218242	1.882938
8 H	-0.196555	-4.636636	4.471960
9 N	0.886365	-1.298793	-0.748797
10 C	1.797550	-2.257144	-1.495643
11 C	3.254355	-1.939445	-1.116539
12 C	1.623986	-2.202538	-3.025995
13 C	-0.621672	-1.355137	-0.987338
14 C	-1.066562	-0.580868	-2.243176
15 C	-1.148420	-2.793675	-0.935169
16 H	1.209213	-0.337279	-0.958727
17 H	7.086084	-0.798903	0.995821
18 H	7.398423	-1.096322	2.715281
19 H	6.666432	0.442939	2.201190
20 H	4.265161	-1.004775	5.383091
21 H	6.858892	-2.398039	4.489269
22 H	5.308553	-3.213414	4.792017
23 H	6.154998	-2.386230	6.119950
24 H	6.219045	0.181987	6.218721
25 H	6.971468	0.223980	4.611977
26 H	1.547738	-3.264563	-1.134269
27 H	3.929109	-2.647313	-1.615540
28 H	3.407513	-2.028898	-0.037477
29 H	3.522889	-0.918221	-1.421679
30 H	2.388745	-2.839644	-3.492011
31 H	1.760395	-1.176772	-3.396523
32 H	0.644948	-2.567554	-3.350346
33 H	-1.038275	-0.811582	-0.128619
34 H	-0.605521	0.416876	-2.267923
35 H	-2.156905	-0.444364	-2.199858
36 H	-0.827262	-1.101349	-3.176007
37 C	4.389720	2.475088	2.217383
38 H	-0.812084	-3.304169	-0.022677
39 H	-2.246763	-2.771231	-0.929601
40 H	5.468917	1.131466	4.903111
41 O	1.616403	-2.122767	3.416338
42 C	1.768721	-3.362046	3.066442
43 C	1.969874	-4.434501	4.145145
44 C	2.236581	-3.787314	5.521097
45 C	3.152691	-5.348237	3.734715
46 C	0.658631	-5.268757	4.192999

47 O	1.718755	-3.683338	1.832017
48 N	4.585289	-0.869528	3.371579
49 C	5.290829	-1.259937	2.128674
50 C	5.334585	-2.778535	1.813635
51 C	6.693646	-0.636459	2.010059
52 C	5.156695	-1.021610	4.734067
53 C	5.914401	-2.336106	5.046328
54 C	6.008637	0.204795	5.138381
55 H	3.649572	-1.279908	3.360569
56 H	2.395728	-4.573883	6.272738
57 H	3.128163	-3.150766	5.491549
58 H	1.388446	-3.166336	5.836661
59 H	3.253137	-6.168296	4.460415
60 H	4.095744	-4.788681	3.716319
61 H	2.986104	-5.773402	2.736978
62 C	0.815976	0.436966	1.538598
63 O	-0.250815	0.980790	1.617427
64 H	4.506840	1.455557	2.605006
65 O	2.251147	1.298890	-0.583808
66 H	5.950972	2.505815	-0.077390
67 H	2.774172	4.337728	0.903320
68 H	3.258421	3.925989	-0.766221
69 H	4.467091	4.557424	0.388792
70 H	5.286629	0.866359	0.102792
71 H	5.350362	3.004136	2.298050
72 H	4.720386	1.904894	-1.226330
73 C	2.665798	1.627077	0.526298
74 O	2.035412	1.307109	1.686500
75 C	3.933372	2.474281	0.741891
76 C	5.041386	1.897194	-0.176929
77 C	3.579471	3.917487	0.284266
78 H	-0.828562	-3.382738	-1.804469
79 H	3.658196	2.992846	2.852631

Amine palladium anhydride κ² pivalate with external amine **Int-14k**



DZP:

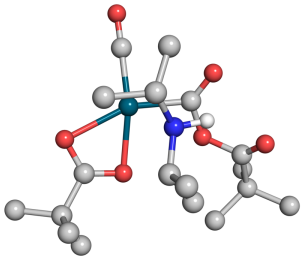
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9671.22	465.813	287.518	-9318.44

Atom	X	Y	Z
1 Pd	1.598802	-1.114757	0.801818
2 H	4.464369	-5.907571	2.428662
3 H	4.760673	-4.450684	1.442199
4 H	-0.642187	1.753885	3.350380
5 H	-0.795484	0.659903	6.217658
6 H	-0.854607	2.361840	5.710112
7 H	0.636980	1.412139	5.461666
8 H	3.300530	-5.438007	1.156126
9 N	-0.102546	-0.780943	-0.494252
10 C	-0.007955	-1.651765	-1.732735
11 C	1.328156	-1.366355	-2.439691
12 C	-1.184348	-1.454901	-2.708341
13 C	-1.354971	-0.862379	0.383809
14 C	-2.498326	0.038189	-0.116562
15 C	-1.784303	-2.310204	0.646728
16 H	0.000902	0.201134	-0.795002
17 H	-2.911479	1.916494	4.167200
18 H	-2.926933	0.236754	4.735915
19 H	-2.834264	0.576051	2.992186
20 H	0.115785	-2.252363	3.361102
21 H	0.751007	-0.992171	6.092206
22 H	1.899790	-1.166928	4.742394
23 H	1.190384	-2.610198	5.506117
24 H	-1.328916	-3.126081	5.091702
25 H	-1.798246	-1.501753	5.631142
26 H	-0.007137	-2.690236	-1.372121
27 H	1.415854	-1.997211	-3.334368
28 H	2.180751	-1.574860	-1.780911

29 H	1.385602	-0.312627	-2.750819
30 H	-0.999436	-2.047170	-3.615920
31 H	-1.274809	-0.398540	-3.000583
32 H	-2.136534	-1.784089	-2.282600
33 H	-1.027066	-0.458020	1.354895
34 H	-2.136503	1.058035	-0.314164
35 H	-3.256500	0.105999	0.677163
36 H	-2.989936	-0.340086	-1.019697
37 C	5.752344	0.144849	2.295079
38 H	-0.940146	-2.915568	0.999047
39 H	-2.542883	-2.302042	1.441767
40 H	-2.283871	-2.074830	4.014055
41 O	3.063171	-1.884569	2.203629
42 C	2.539457	-3.066362	2.187802
43 C	3.199484	-4.207564	2.973435
44 C	2.098789	-5.074139	3.632344
45 C	4.171875	-3.661137	4.040677
46 C	3.981627	-5.055122	1.928239
47 O	1.501934	-3.295057	1.477203
48 N	-0.334163	-0.255769	3.439566
49 C	-0.958991	0.953303	4.041470
50 C	-0.459923	1.367532	5.446854
51 C	-2.501511	0.912069	3.983051
52 C	-0.169506	-1.549411	4.159910
53 C	0.986239	-1.575094	5.192736
54 C	-1.477143	-2.088066	4.759661
55 H	0.603011	0.033380	3.149376
56 H	2.560218	-5.921456	4.160188
57 H	1.522299	-4.486701	4.358857
58 H	1.404151	-5.461404	2.876381
59 H	4.657195	-4.500231	4.561089
60 H	3.639866	-3.054587	4.783993
61 H	4.949476	-3.036830	3.584023
62 C	2.159438	0.772261	0.494726
63 O	1.713977	1.611040	-0.250849
64 H	5.920029	0.639448	1.329981
65 O	2.350465	1.167267	3.198961
66 H	6.299423	2.402129	3.821602
67 H	4.283597	-0.742638	4.450318
68 H	3.938134	0.828709	5.207662
69 H	5.626835	0.257741	5.069486

70 H	5.385719	2.918951	2.377871
71 H	6.720201	0.044694	2.807491
72 H	4.625681	2.999961	3.992585
73 C	3.388081	1.058422	2.567654
74 O	3.418701	1.074488	1.186976
75 C	4.788894	0.960993	3.188273
76 C	5.304937	2.418699	3.353143
77 C	4.646830	0.283642	4.572177
78 H	-2.226075	-2.790045	-0.237798
79 H	5.341182	-0.854266	2.107857

Carbonyl palladium anhydride κ^2 pivalate with external amine **Int-14l**



DZP:

Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7399.51	334.828	244.632	-7160.86

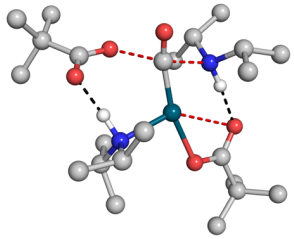
Atom	X	Y	Z
1 Pd	0.099287	-0.045965	1.260147
2 H	-3.014714	-3.744645	-2.161015
3 H	-2.390408	-2.071669	-2.209995
4 H	-2.240475	4.525049	-1.233584
5 O	-0.537848	1.929424	-0.528658
6 H	-2.247931	3.805604	-4.329385
7 H	-0.994987	-4.832008	0.854045
8 H	-3.495129	-2.570443	-0.908033
9 N	2.473692	-0.108281	-0.791355
10 C	3.618550	-0.544338	0.055240
11 C	3.334081	-1.925081	0.671744
12 C	3.888520	0.512478	1.137059
13 C	2.208256	-0.925394	-2.009294
14 C	3.445412	-1.176431	-2.902402
15 C	1.086689	-0.255526	-2.814122
16 H	2.634434	0.865161	-1.083045
17 H	-2.225095	0.783699	-2.025817
18 H	-1.431591	0.952951	-3.609517

19 H	-3.093116	1.553985	-3.388020
20 H	-2.862263	2.938051	-0.704134
21 H	-3.544788	3.728263	-2.150137
22 H	-0.949337	4.694813	-3.487860
23 C	-0.275929	2.686389	-1.728841
24 H	-0.034815	-2.999336	-2.331034
25 C	0.427015	1.803707	0.453454
26 H	4.541172	-0.625711	-0.552285
27 H	4.138215	-2.200656	1.368937
28 H	3.272166	-2.709979	-0.094538
29 H	2.380255	-1.912536	1.218196
30 H	4.786672	0.241913	1.709860
31 H	3.044816	0.590635	1.831434
32 H	4.046884	1.505914	0.693028
33 H	1.836773	-1.894943	-1.651736
34 H	4.226395	-1.747066	-2.382771
35 H	3.878092	-0.219645	-3.234326
36 H	3.153036	-1.749109	-3.795116
37 H	1.408912	0.730192	-3.182367
38 H	0.199176	-0.135229	-2.189045
39 H	0.817392	-0.870868	-3.684513
40 H	0.595758	-4.067314	-1.045912
41 O	-0.956654	-0.981462	-0.405231
42 C	-0.923322	-2.159032	0.122942
43 C	-1.454362	-3.348559	-0.692401
44 C	-1.850828	-4.506443	0.249934
45 C	-0.296953	-3.800166	-1.628549
46 C	-2.664657	-2.902039	-1.547472
47 O	-0.411145	-2.326992	1.280807
48 O	0.824551	3.059370	-2.036708
49 C	-1.590385	2.845550	-2.499082
50 C	-1.316430	3.695465	-3.757964
51 C	-2.114937	1.436194	-2.900128
52 C	-2.622123	3.553853	-1.579304
53 H	-0.565539	3.216797	-4.399825
54 O	1.282916	2.602031	0.725661
55 H	-0.611344	-4.681590	-2.206532
56 H	-2.209100	-5.359177	-0.344223
57 H	-2.653646	-4.196885	0.934004
58 C	0.657239	0.571856	3.013074
59 O	0.977718	0.925926	4.059029

A1.3F Initial carbamoyl formation transition states

Calculations in this section were performed as before, with the exception that DFT vibrational analysis was performed using a TZP basis set for palladium and DZP for all other atoms.

Carbamoyl formation from bisamine palladium anhydride pivalate due to migration of the pivalate bonded amine **TS-9b**



Imaginary frequency at -123 kcal/mol

DZP:

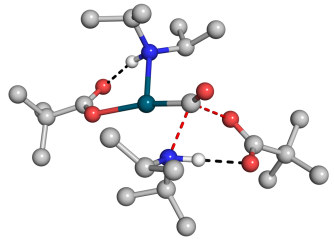
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9661.94	464.504	280.409	-9307.68

Atom	X	Y	Z
1 Pd	0.256058	-0.339552	-0.356171
2 H	-0.287990	-6.429417	0.960651
3 H	0.220584	-5.394353	-0.398183
4 H	-2.736402	1.589841	-0.554287
5 H	-3.260532	1.127233	1.843427
6 H	-1.572654	0.757818	1.471917
7 H	-2.757481	-0.576488	1.628413
8 H	-1.467018	-5.335903	0.177653
9 N	2.194223	0.521454	0.102257
10 C	2.601716	0.422740	1.563222
11 C	3.332241	-0.885377	1.895400
12 C	1.375555	0.630394	2.469374
13 C	3.284681	0.232589	-0.903543
14 C	4.485784	1.181009	-0.691265
15 C	2.726049	0.389811	-2.327243
16 H	1.910261	1.533817	-0.055796
17 H	-4.710212	0.345293	-1.519878
18 H	-5.006394	1.044931	0.078375
19 H	-4.725518	-0.702673	-0.067282
20 H	-2.866847	0.008280	-2.886284
21 H	-4.212023	-1.877525	-1.757230
22 H	-2.756908	-2.891142	-1.805918
23 H	-3.554803	-2.389800	-3.321722

24 H	-0.531076	-1.987052	-2.683811
25 H	-1.446775	-1.667847	-4.170586
26 H	3.280562	1.275849	1.731168
27 H	3.521750	-0.921977	2.977708
28 H	4.302339	-0.964683	1.387960
29 H	2.712010	-1.743979	1.619585
30 H	1.714875	0.793275	3.502290
31 H	0.729765	-0.257806	2.455406
32 H	0.786387	1.499233	2.158404
33 H	3.598480	-0.809746	-0.756884
34 H	4.966066	1.034528	0.283669
35 H	4.151799	2.225908	-0.764253
36 H	5.239783	0.996371	-1.468434
37 H	2.302176	1.394125	-2.465297
38 H	1.942888	-0.352275	-2.528428
39 H	3.531166	0.243591	-3.060099
40 H	-0.474388	-0.374811	-3.453475
41 O	0.703027	-2.200801	0.597419
42 C	-0.326602	-2.964126	0.801381
43 C	-0.046268	-4.323748	1.501978
44 C	-0.962124	-4.416699	2.748598
45 C	1.431464	-4.463268	1.922531
46 C	-0.421263	-5.441909	0.494176
47 O	-1.510688	-2.694498	0.468148
48 N	-1.970686	-0.348553	-0.996514
49 C	-2.942087	0.566432	-0.218310
50 C	-2.605076	0.453031	1.275947
51 C	-4.431814	0.278552	-0.461699
52 C	-2.361453	-0.835186	-2.396456
53 C	-3.287415	-2.068336	-2.305238
54 C	-1.118327	-1.226972	-3.219301
55 H	-1.890781	-1.233830	-0.420754
56 H	-0.828815	-5.392064	3.239906
57 H	-2.014818	-4.302397	2.461149
58 H	-0.713608	-3.629251	3.475574
59 H	1.593031	-5.444074	2.394903
60 H	1.711583	-3.682251	2.641750
61 H	2.099573	-4.377223	1.055759
62 C	-0.536511	1.088926	-1.339075
63 O	-0.884113	1.748280	-2.233280
64 H	2.387017	4.318389	1.970752

65 O	-0.623020	2.708606	0.368261
66 H	0.971852	6.854755	0.784036
67 H	-1.374525	4.298535	2.307595
68 H	-1.706659	5.210604	0.824356
69 H	-0.982491	6.041900	2.230058
70 H	1.034793	3.793921	3.007510
71 H	1.455552	5.522148	2.912541
72 H	1.921534	5.670259	-0.164207
73 C	0.430668	3.424872	0.332597
74 O	1.523102	3.126538	-0.249376
75 C	0.413076	4.770629	1.137963
76 C	0.923041	5.909220	0.222458
77 C	-0.999913	5.101036	1.658612
78 C	1.386111	4.588766	2.333032
79 H	0.246535	6.053778	-0.633502

Carbamoyl formation from bisamine palladium anhydride pivalate due to migration of the anhydride bonded amine **TS-9c**



Imaginary frequency at -124 cm^{-1}

DZP:

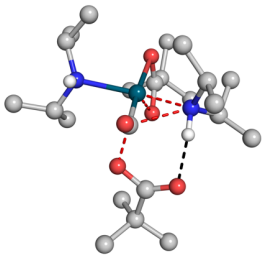
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9662.37	463.896	276.569	-9307.21

Atom	X	Y	Z
1 Pd	0.176194	-0.852426	0.347751
2 H	0.180198	-6.590370	1.910303
3 H	1.025301	-5.103689	1.391589
4 H	-2.236341	1.067270	2.982385
5 H	-0.076000	1.918320	3.742827
6 H	-0.136004	2.147003	1.977371
7 H	0.806091	0.808842	2.662827
8 H	-0.333546	-5.735066	0.433321
9 N	1.974626	-0.852988	-1.249598
10 C	3.375427	-0.975591	-0.632730
11 C	3.319267	-1.089552	0.895775
12 C	4.268472	0.183758	-1.102334

13 C	1.581130	-2.043853	-2.159641
14 C	2.466968	-2.080545	-3.421638
15 C	1.588306	-3.390468	-1.428425
16 H	2.028716	-0.081247	-1.964320
17 H	-2.111887	-1.286342	3.795993
18 H	-1.063471	-0.225944	4.778735
19 H	-0.353111	-1.296491	3.542339
20 H	-2.456680	0.065140	-0.505487
21 H	-4.167471	0.848716	1.938550
22 H	-4.204952	-0.721833	1.089119
23 H	-4.716687	0.766717	0.251000
24 H	-2.956343	2.467367	-0.491124
25 H	-2.356966	2.640405	1.171023
26 H	3.797820	-1.911662	-1.020511
27 H	4.328470	-1.285111	1.286722
28 H	2.664857	-1.914048	1.209091
29 H	2.956630	-0.154731	1.344313
30 H	5.290212	0.032423	-0.727642
31 H	3.896927	1.144107	-0.723938
32 H	4.304034	0.235618	-2.198668
33 H	0.554220	-1.797919	-2.466528
34 H	3.510946	-2.317579	-3.170755
35 H	2.436659	-1.126687	-3.958894
36 H	2.097256	-2.871419	-4.089880
37 H	2.608022	-3.687933	-1.144004
38 H	0.969187	-3.383157	-0.527725
39 H	1.197432	-4.160704	-2.108423
40 H	-1.240133	2.205055	-0.157866
41 O	0.008495	-2.767543	1.350189
42 C	-1.111619	-3.347575	1.652498
43 C	-0.937892	-4.753095	2.301821
44 C	-2.298303	-5.471341	2.406976
45 C	-0.348540	-4.525484	3.719797
46 C	0.047499	-5.596753	1.455765
47 O	-2.255347	-2.847971	1.501250
48 N	-1.576001	-0.135179	1.373391
49 C	-1.341374	0.471934	2.742162
50 C	-0.115374	1.397580	2.775081
51 C	-1.213506	-0.656089	3.779138
52 C	-2.563197	0.578716	0.460127
53 C	-3.999426	0.351071	0.973013

54 C	-2.247465	2.061142	0.243803
55 H	-1.972608	-1.097574	1.500961
56 H	-2.167060	-6.452204	2.888274
57 H	-2.736379	-5.627279	1.411178
58 H	-3.009243	-4.878841	2.997204
59 H	-0.193600	-5.491625	4.224015
60 H	-1.033190	-3.921866	4.334039
61 H	0.614313	-4.001107	3.656054
62 C	0.838337	0.696616	-0.547905
63 O	1.469333	1.681230	-0.423181
64 H	-1.427629	3.080457	-3.845282
65 O	-0.276546	0.798465	-2.178955
66 H	-0.215519	2.058812	-6.542596
67 H	-1.462043	-0.678536	-4.235012
68 H	0.027609	-0.791495	-5.212563
69 H	-1.456939	-0.112156	-5.928913
70 H	-2.314885	1.594311	-3.441723
71 H	-2.317815	2.207703	-5.120930
72 H	1.281678	1.347476	-5.874641
73 C	0.411899	1.032942	-3.256869
74 O	1.665087	1.009088	-3.329993
75 C	-0.448646	1.246036	-4.537066
76 C	0.389462	1.938008	-5.631728
77 C	-0.861350	-0.177231	-5.006218
78 C	-1.707910	2.082681	-4.213694
79 H	0.721807	2.932129	-5.299974

Carbamoyl formation from bisamine palladium anhydride pivalate due to anhydride bonded amine migration with concerted κ^2 pivalate binding **TS-9d**



Imaginary frequency at -74 kcal/mol

DZP:

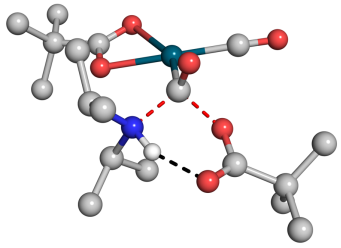
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9658.26	465.750	279.501	-9302.40

Atom	X	Y	Z
1 Pd	0.589094	-0.986529	0.194396

2 H	-1.133457	-6.566194	0.968842
3 H	0.388405	-5.637254	0.962484
4 H	-1.605229	1.909423	1.769509
5 H	-0.638919	4.026860	1.008218
6 H	-1.571430	3.287638	-0.314174
7 H	0.208669	3.215779	-0.329991
8 H	-0.772144	-5.436984	-0.372221
9 N	2.701122	-1.887578	-0.040521
10 C	3.411755	-2.340117	1.226995
11 C	2.961154	-3.717380	1.728571
12 C	3.211346	-1.258453	2.301165
13 C	2.885558	-2.710408	-1.312201
14 C	4.360164	-3.075817	-1.565256
15 C	1.957734	-3.928882	-1.394678
16 H	3.159485	-0.992360	-0.258097
17 H	0.428844	0.742964	2.587200
18 H	0.545046	2.514110	2.742773
19 H	1.425937	1.673805	1.439560
20 H	-2.322131	-0.859410	-0.262948
21 H	-2.806416	0.395677	2.502315
22 H	-1.720287	-0.992459	2.226466
23 H	-3.448479	-1.118325	1.842670
24 H	-4.428432	0.445286	-0.014547
25 H	-3.521960	1.875088	0.518358
26 H	4.488879	-2.385110	0.989948
27 H	3.416206	-3.899811	2.713148
28 H	3.281946	-4.524511	1.061301
29 H	1.873647	-3.742362	1.841198
30 H	3.863124	-1.470269	3.160988
31 H	2.169199	-1.246834	2.642867
32 H	3.465594	-0.259082	1.919225
33 H	2.566095	-2.011245	-2.099596
34 H	4.459857	-3.494571	-2.576786
35 H	4.720932	-3.831468	-0.853800
36 H	5.011301	-2.191808	-1.498742
37 H	2.244881	-4.720364	-0.694386
38 H	0.920368	-3.645871	-1.196205
39 H	2.016657	-4.345268	-2.411130
40 H	-3.312299	1.249986	-1.144952
41 O	-0.001775	-2.472210	1.882949
42 C	-0.725799	-3.130426	1.042560

43 C	-1.388105	-4.454035	1.488092
44 C	-2.887574	-4.407821	1.103012
45 C	-1.232686	-4.676531	3.006708
46 C	-0.680946	-5.597022	0.710079
47 O	-0.862933	-2.720663	-0.146317
48 N	-0.954069	0.657465	0.191127
49 C	-0.726030	1.864780	1.116613
50 C	-0.676937	3.175114	0.313671
51 C	0.498131	1.681859	2.023732
52 C	-2.344597	0.022415	0.387732
53 C	-2.580441	-0.445089	1.830842
54 C	-3.462548	0.965686	-0.096364
55 H	-1.023002	1.009762	-0.777976
56 H	-3.369999	-5.368387	1.339252
57 H	-2.998266	-4.202254	0.030685
58 H	-3.406503	-3.615725	1.662016
59 H	-1.711240	-5.623545	3.299288
60 H	-1.700807	-3.858922	3.572241
61 H	-0.172866	-4.716163	3.290839
62 C	0.978199	0.351126	-1.118244
63 O	1.494253	1.419092	-1.202779
64 H	-2.590465	0.117435	-4.960031
65 O	0.644444	-0.345121	-2.598259
66 H	-0.236934	-1.565981	-6.227857
67 H	-1.271142	-2.727364	-2.734712
68 H	0.326867	-2.756294	-3.489635
69 H	-1.096296	-3.289858	-4.426831
70 H	-3.088516	-1.105036	-3.772393
71 H	-2.675460	-1.601597	-5.437156
72 H	1.042766	-0.974826	-5.132795
73 C	-0.587579	-0.146324	-3.070125
74 O	-1.377120	0.694194	-2.622397
75 C	-0.945249	-1.122730	-4.212988
76 C	-0.009879	-0.854888	-5.420408
77 C	-0.734764	-2.566666	-3.680398
78 C	-2.417857	-0.912196	-4.620364
79 H	-0.151724	0.164358	-5.807980

Carbamoyl formation from carbonyl palladium anhydride κ² pivalate external amine **TS-9e**



DZP:

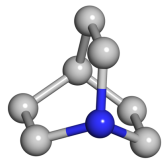
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-7392.19	335.217	242.269	-7152.22

Atom	X	Y	Z
1 Pd	-0.384027	-0.354914	0.949051
2 H	-0.539332	-5.821400	-1.313573
3 H	-0.019443	-4.156889	-1.702932
4 H	0.175007	5.194404	0.109713
5 O	-0.028784	2.064817	-0.673071
6 H	-0.629412	6.018098	-2.820910
7 H	-1.014205	-5.215052	2.399030
8 H	-1.715781	-4.482497	-1.258621
9 N	1.786499	0.335180	-1.268311
10 C	3.182735	-0.257737	-0.921217
11 C	3.209989	-1.101569	0.357872
12 C	4.229485	0.864602	-0.936056
13 C	1.030881	-0.529979	-2.306971
14 C	1.735271	-0.356625	-3.667122
15 C	-0.457708	-0.191102	-2.452979
16 H	1.962602	1.260746	-1.743420
17 H	-2.297775	2.861769	-1.570201
18 H	-1.708827	3.119114	-3.234078
19 H	-2.579875	4.422291	-2.390745
20 H	-1.204811	4.103614	0.392044
21 H	-1.456480	5.671158	-0.426679
22 H	1.023182	5.583002	-2.306100
23 C	0.454163	2.987514	-1.504633
24 H	1.833501	-4.331068	0.054453
25 C	1.037445	0.994751	0.044653
26 H	3.387762	-0.931372	-1.760906
27 H	4.182173	-1.613779	0.395698
28 H	2.419694	-1.858039	0.351341
29 H	3.108111	-0.480098	1.253552

30 H	5.225516	0.422029	-0.797972
31 H	4.045127	1.581244	-0.128393
32 H	4.222944	1.403101	-1.894121
33 H	1.123533	-1.554970	-1.935668
34 H	2.795351	-0.636115	-3.644657
35 H	1.655582	0.686167	-4.006186
36 H	1.237558	-0.996797	-4.407554
37 H	-0.607343	0.806616	-2.879133
38 H	-0.996233	-0.248318	-1.502605
39 H	-0.897126	-0.930804	-3.136329
40 H	1.437759	-4.745854	1.741563
41 O	0.281142	-2.219060	0.074253
42 C	-0.486429	-3.028625	0.741917
43 C	-0.319699	-4.531991	0.438104
44 C	-1.249653	-5.371472	1.337701
45 C	1.161294	-4.920162	0.691465
46 C	-0.670790	-4.760072	-1.056424
47 O	-1.318022	-2.597928	1.588901
48 O	1.551555	2.912707	-2.081897
49 C	-0.529009	4.162297	-1.698110
50 C	0.072536	5.183719	-2.684268
51 C	-1.863725	3.599083	-2.256671
52 C	-0.768863	4.821058	-0.313632
53 H	0.263815	4.722214	-3.662351
54 O	1.795871	1.536376	0.827090
55 H	1.309688	-5.987157	0.468584
56 H	-1.126741	-6.439211	1.104462
57 H	-2.301181	-5.096283	1.182053
58 C	-1.233923	1.193047	1.757165
59 O	-1.786334	2.092672	2.216364

A1.4 Quinuclidine modelling

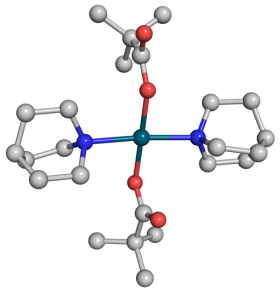
Quinuclidine



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-2617.54	125.422	87.614	-2526.56

Atom	X	Y	Z
1 N	0.000000	0.000000	2.355411
2 C	-1.400017	0.000000	1.845083
3 C	-1.454546	0.000000	0.275404
4 C	0.000000	0.000000	-0.256706
5 C	0.727273	-1.259674	0.275404
6 C	0.700008	-1.212450	1.845083
7 C	0.700008	1.212450	1.845083
8 C	0.727273	1.259674	0.275404
9 H	-1.904393	0.886929	2.256308
10 H	-1.904393	-0.886929	2.256308
11 H	-1.988752	0.887787	-0.098246
12 H	-1.988752	-0.887787	-0.098246
13 H	0.000000	0.000000	-1.357077
14 H	1.763222	-1.278416	-0.098246
15 H	0.225530	-2.166203	-0.098246
16 H	1.720299	-1.205788	2.256308
17 H	0.184093	-2.092717	2.256308
18 H	1.720299	1.205788	2.256308
19 H	0.184093	2.092717	2.256308
20 H	1.763222	1.278416	-0.098246
21 H	0.225530	2.166203	-0.098246

Bisquinuclidine palladium dipivalate **Int-21**



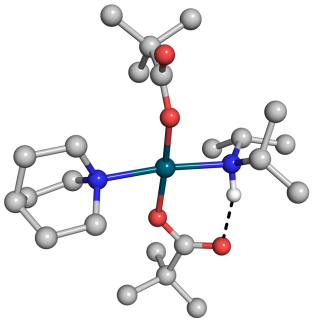
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9422.75	443.152	261.871	-9082.55

Atom	X	Y	Z
1 Pd	-0.171662	-2.543115	-0.704295
2 H	0.152488	-2.823747	3.604956
3 H	-0.703971	-2.063387	2.261064
4 C	-1.338240	0.145599	0.207927
5 C	-2.401800	1.276562	0.068399
6 H	-2.634050	-2.041860	1.225975
7 H	-3.377693	-2.510030	-0.295459

8 H	0.647414	-3.154608	1.937654
9 N	1.377037	-3.997128	-1.179423
10 C	1.667748	-4.936910	-0.030640
11 H	3.775253	-0.583013	-3.063775
12 C	2.525081	-6.151730	-0.499643
13 C	0.823083	-4.805492	-2.339586
14 C	1.911885	-5.772924	-2.901019
15 H	0.870954	0.678785	-5.150694
16 C	2.681960	-3.367874	-1.618826
17 H	-2.440513	-1.707023	-2.419566
18 H	-1.430833	-0.265341	-2.380440
19 H	-4.090359	-0.238818	1.538541
20 C	1.024396	-0.834281	-2.805009
21 H	-5.062344	-0.949409	0.245186
22 H	-3.409129	0.968486	-2.556829
23 C	1.835914	0.440308	-3.198918
24 O	0.922801	-0.989249	-1.506945
25 H	-2.938739	-2.978537	3.173402
26 H	0.712335	-5.262165	0.371495
27 H	0.109751	1.770618	-2.910847
28 H	1.679227	2.596705	-2.880433
29 H	1.157593	1.629970	-1.482672
30 H	3.337465	-6.329710	0.214758
31 H	2.457510	1.473358	-5.009869
32 H	1.910872	-7.059840	-0.533007
33 H	0.487081	-4.091429	-3.093821
34 C	3.090078	-5.840454	-1.901688
35 H	2.268857	-5.419762	-3.876221
36 H	1.479237	-6.768994	-3.050693
37 H	2.347020	-0.293566	-5.197506
38 H	3.261048	0.190900	-1.549950
39 H	3.870577	1.181142	-2.900164
40 H	-4.416135	-0.433355	-2.175352
41 O	-1.319306	-4.093563	0.044516
42 C	-1.767718	-4.589311	1.172623
43 C	-1.190388	-4.184575	2.580122
44 C	-0.454611	-5.439035	3.132760
45 C	-2.388638	-3.864665	3.514001
46 C	-0.217666	-2.988796	2.584584
47 O	-2.658392	-5.458014	1.152711
48 H	-1.124452	-6.304276	3.140133

49 H	-2.026477	-3.663386	4.530387
50 H	-0.382437	0.428986	-0.230700
51 H	-1.168230	-0.116397	1.255761
52 H	-3.087515	-4.704813	3.546767
53 H	-2.538312	1.776625	1.034353
54 H	-4.536554	1.395837	-0.383891
55 H	-2.060792	2.034097	-0.648425
56 H	-0.113601	-5.248392	4.158560
57 H	0.425844	-5.687470	2.529071
58 N	-1.803618	-1.117924	-0.484546
59 C	-2.994879	-1.660783	0.273375
60 C	-2.262435	-0.768841	-1.890188
61 C	-4.070078	-0.552020	0.487294
62 C	-3.731398	0.653600	-0.416612
63 C	-3.533082	0.133639	-1.857006
64 C	1.879688	0.581856	-4.734429
65 C	3.275156	0.296771	-2.639239
66 C	1.151625	1.683965	-2.575495
67 O	0.548523	-1.601439	-3.656762
68 C	3.774724	-4.456360	-1.842221
69 H	2.184894	-4.350448	0.733793
70 H	-0.046201	-5.344204	-1.954654
71 H	2.972670	-2.633915	-0.864856
72 H	2.472351	-2.835567	-2.544899
73 H	3.807116	-6.610576	-2.207094
74 H	4.511946	-4.439537	-1.029881
75 H	4.310695	-4.248080	-2.775670

Mo*noquinuclidine monodiisopropylamine palladium dipivalate* **Int-22**



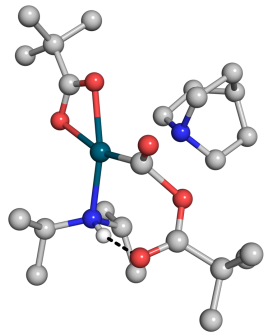
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9416.67	450.413	260.357	-9068.62

Atom	X	Y	Z
1 Pd	-0.214790	-2.596808	-0.687111
2 H	0.579598	-3.162015	1.895080

3 H	0.180434	-2.938251	3.604302
4 C	-1.321345	0.100615	0.254374
5 C	-2.367343	1.255892	0.180101
6 H	-2.701429	-2.014954	1.249675
7 H	-3.411550	-2.513590	-0.278029
8 H	-0.789368	-2.142664	2.359772
9 N	1.335632	-3.996454	-1.171145
10 C	2.443428	-4.152705	-0.152701
11 C	2.918541	-2.765324	0.320593
12 C	3.658059	-4.934012	-0.701058
13 C	0.729679	-5.255088	-1.802118
14 C	1.452120	-5.622906	-3.114061
15 C	0.596784	-6.439277	-0.837563
16 H	1.723476	-3.436768	-1.956767
17 H	-2.518686	-1.689843	-2.377683
18 H	-1.372553	-0.342710	-2.359521
19 H	-4.217806	-0.252517	1.492297
20 C	1.692803	-1.056745	-2.515525
21 H	-5.088190	-0.902688	0.099118
22 H	-3.206774	1.111487	-2.482748
23 C	2.220308	0.359324	-2.904196
24 O	0.822791	-1.024097	-1.546224
25 H	-2.923609	-3.225497	3.356055
26 H	2.014835	-4.695314	0.696774
27 H	3.383951	-2.217604	-0.506260
28 H	3.662501	-2.887836	1.115359
29 H	2.097063	-2.154423	0.703405
30 H	4.447248	-4.949014	0.059733
31 H	4.056478	-4.440507	-1.595760
32 H	3.420450	-5.968847	-0.952851
33 H	-0.287174	-4.950986	-2.067953
34 H	2.458666	-6.015067	-2.941660
35 H	1.529439	-4.751229	-3.773842
36 H	0.872799	-6.394735	-3.635270
37 H	1.563686	-6.867576	-0.555617
38 H	0.054108	-6.154816	0.063875
39 H	0.018945	-7.226773	-1.334494
40 H	-4.345547	-0.221620	-2.255567
41 O	-1.405917	-4.096441	0.065233
42 C	-1.820009	-4.623955	1.190353
43 C	-1.166775	-4.296716	2.579913

44 C	-0.334441	-5.548972	2.974811
45 C	-2.306237	-4.096014	3.612779
46 C	-0.247049	-3.062299	2.600760
47 O	-2.734866	-5.467283	1.169678
48 H	-0.957977	-6.448439	2.957843
49 H	-1.880760	-3.925862	4.610173
50 H	-0.373149	0.378764	-0.205318
51 H	-1.124772	-0.195131	1.288277
52 H	-2.957836	-4.973013	3.649983
53 H	-2.530487	1.676081	1.179531
54 H	-4.470230	1.466560	-0.362537
55 H	-1.995159	2.066158	-0.459164
56 H	0.074647	-5.422520	3.985484
57 H	0.507655	-5.698536	2.288454
58 N	-1.825727	-1.134851	-0.459855
59 C	-3.038146	-1.652484	0.278743
60 C	-2.250524	-0.761227	-1.867307
61 C	-4.113494	-0.532118	0.436709
62 C	-3.689015	0.698879	-0.394132
63 C	-3.441344	0.247418	-1.849669
64 C	3.119551	0.264826	-4.154060
65 C	3.039954	0.898740	-1.701517
66 C	1.022122	1.301056	-3.184841
67 O	2.117134	-2.086469	-3.080244
68 H	3.498128	1.261097	-4.415702
69 H	2.563606	-0.131323	-5.011298
70 H	3.972623	-0.397504	-3.975385
71 H	2.416349	0.966515	-0.803957
72 H	3.432869	1.897009	-1.933133
73 H	3.890861	0.242235	-1.480644
74 H	0.398436	0.912288	-3.999824
75 H	1.386477	2.292843	-3.481111
76 H	0.393769	1.415921	-2.296394

Diisopropylamine palladium anhydride κ² anhydride palladium anhydride with external quinuclidine **Int-23**



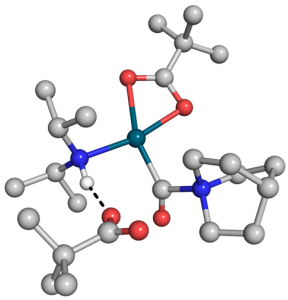
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9746.93	456.949	282.499	-9401.05

Atom	X	Y	Z
1 Pd	1.001298	-1.002963	0.662240
2 H	-0.516898	-3.227240	5.865207
3 H	-0.054435	-1.638683	5.206662
4 H	1.385898	4.787916	-3.322813
5 H	3.646453	2.682748	-3.840606
6 H	2.436990	3.204032	-5.038304
7 H	2.645345	1.479986	-4.669076
8 H	1.019681	-3.037988	4.993354
9 N	1.967434	-1.545400	-1.172478
10 C	2.970774	-2.655272	-0.924521
11 C	4.003652	-2.164295	0.105995
12 C	3.687091	-3.128358	-2.206042
13 C	0.866170	-1.743193	-2.212145
14 C	1.324609	-1.474015	-3.660995
15 C	0.166385	-3.098930	-2.054569
16 H	2.494256	-0.696740	-1.436884
17 C	1.573002	2.622559	-3.132629
18 C	1.606143	4.057602	-2.534467
19 C	2.645024	2.486492	-4.235532
20 O	0.881117	1.493274	-1.120584
21 H	-0.023207	2.992788	-4.564721
22 H	2.594964	4.287671	-2.120145
23 C	1.892710	1.649844	-1.969017
24 C	1.293543	0.906633	0.389884
25 H	-2.284508	-1.506234	3.898213
26 H	2.405840	-3.490546	-0.496181
27 H	4.717811	-2.966354	0.321566
28 H	3.524017	-1.866011	1.044707

29 H	4.559858	-1.302330	-0.283522
30 H	4.470951	-3.842898	-1.930334
31 H	4.161069	-2.285351	-2.722778
32 H	3.012631	-3.630686	-2.902215
33 H	0.148432	-0.960907	-1.951906
34 H	1.877616	-2.310109	-4.095602
35 H	1.951598	-0.579480	-3.720878
36 H	0.435474	-1.303915	-4.280167
37 H	0.807097	-3.931091	-2.365991
38 H	-0.148989	-3.267528	-1.020826
39 H	-0.725254	-3.111732	-2.691082
40 H	-0.611428	2.491380	-2.965327
41 O	0.034941	-1.047691	2.604425
42 C	-0.067388	-2.332695	2.556118
43 C	-0.760280	-3.077506	3.703232
44 C	-0.714697	-4.601215	3.462004
45 C	-2.235710	-2.592659	3.774570
46 C	-0.028825	-2.717748	5.025532
47 O	0.405356	-2.947209	1.532402
48 H	-1.217201	-4.869166	2.526470
49 H	-2.735457	-3.066203	4.628140
50 H	0.092534	1.292136	-4.065602
51 C	0.168085	2.327704	-3.713934
52 H	-2.787362	-2.863106	2.866473
53 O	2.993010	1.091570	-1.841921
54 O	1.554554	1.791035	1.132887
55 H	0.861900	4.166105	-1.738570
56 H	-1.218060	-5.118515	4.287707
57 H	0.318117	-4.961562	3.404736
58 N	-1.943154	-0.447591	-0.360267
59 C	-2.678625	-1.709723	-0.095431
60 C	-2.384052	0.106081	-1.665371
61 C	-4.220119	-1.460185	0.054389
62 C	-4.501978	0.024734	-0.291914
63 C	-3.938054	0.328421	-1.704104
64 C	-2.246642	0.541295	0.711481
65 C	-3.768329	0.919591	0.737063
66 H	-2.254736	-2.163134	0.805230
67 H	-2.472445	-2.392593	-0.926261
68 H	-2.071039	-0.588681	-2.455326
69 H	-1.838427	1.041306	-1.819518

70 H	-4.550777	-1.670166	1.080494
71 H	-4.787898	-2.121257	-0.613475
72 H	-4.176099	1.360946	-1.990935
73 H	-4.408938	-0.332854	-2.443690
74 H	-1.620973	1.422877	0.533272
75 H	-1.928067	0.103353	1.661262
76 H	-3.913640	1.977533	0.481454
77 H	-4.189055	0.765325	1.739355
78 H	-5.580456	0.221033	-0.266211

Diisopropylamine κ^2 anhydride activated palladium anhydride with external pivalate **Int-24**



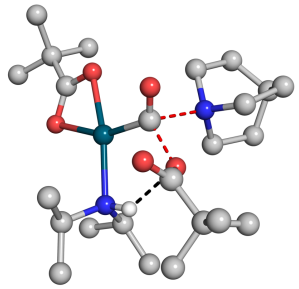
Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9749.01	458.225	275.844	-9399.23

Atom	X	Y	Z
1 N	-0.955804	3.284026	-0.226926
2 C	-1.813481	3.605836	0.978238
3 C	-2.607970	2.338758	1.386923
4 C	-1.963843	1.101992	0.716976
5 C	-0.437450	1.141646	0.963884
6 C	0.168602	2.340928	0.179870
7 C	-1.812613	2.614993	-1.292591
8 C	-2.207951	1.193988	-0.806797
9 H	-2.473150	4.418026	0.672952
10 H	-1.128036	3.943665	1.763874
11 H	-3.650509	2.448937	1.056277
12 H	-2.603966	2.236430	2.480893
13 H	-2.391718	0.175694	1.124826
14 H	0.036951	0.208088	0.628936
15 H	-0.232922	1.248714	2.038454
16 H	0.656729	2.035294	-0.753202
17 H	0.881297	2.910255	0.781516
18 H	-1.225890	2.602448	-2.215499
19 H	-2.687187	3.260151	-1.408871
20 H	-1.622979	0.422430	-1.328384

21 H	-3.268424	1.026560	-1.042273
22 C	-0.220283	4.692579	-0.877560
23 O	0.084824	4.576431	-2.022431
24 Pd	0.384783	6.022176	0.485290
25 N	-0.977286	7.534217	-0.236744
26 H	-1.697452	6.956365	-0.754445
27 O	-2.699424	5.725846	-1.282833
28 C	-3.951643	5.441110	-1.275521
29 O	-4.457435	4.420648	-0.734001
30 C	-4.895169	6.481817	-1.980938
31 C	-6.309479	5.896985	-2.174823
32 C	-4.292315	6.876959	-3.349069
33 C	-4.970979	7.730699	-1.066508
34 C	-0.306510	8.492143	-1.205533
35 C	0.306385	7.705088	-2.373464
36 C	-1.286112	9.558063	-1.740079
37 C	-1.744405	8.198354	0.900099
38 C	-2.483124	7.134018	1.726403
39 C	-0.872808	9.098954	1.778043
40 O	1.634415	6.956354	2.169539
41 C	2.142489	5.790689	2.343477
42 O	1.824811	4.818684	1.542518
43 C	3.082915	5.500523	3.518898
44 C	3.980178	4.284319	3.197669
45 C	2.171199	5.184232	4.741505
46 C	3.948579	6.747088	3.815996
47 H	4.580228	6.998787	2.953315
48 H	-6.271709	4.985036	-2.787689
49 H	-6.960923	6.631086	-2.674523
50 H	-6.755002	5.624394	-1.209844
51 H	-3.273292	7.258253	-3.223539
52 H	-4.907657	7.650718	-3.834836
53 H	-4.243305	6.005719	-4.020234
54 H	-5.641858	8.488746	-1.500093
55 H	-5.350719	7.464063	-0.069231
56 H	-3.978848	8.178992	-0.946527
57 H	0.500357	8.991996	-0.650896
58 H	0.738868	8.406370	-3.100356
59 H	-0.458880	7.098242	-2.875117
60 H	1.099539	7.029268	-2.033122
61 H	-1.669858	10.215304	-0.950897

62 H	-2.137753	9.081583	-2.244537
63 H	-0.761954	10.186596	-2.473158
64 H	-2.514073	8.821013	0.419423
65 H	-1.770643	6.492547	2.263246
66 H	-3.107824	6.503044	1.085513
67 H	-3.125552	7.631360	2.466442
68 H	-0.355990	9.873897	1.197472
69 H	-0.127159	8.510623	2.311897
70 H	-1.512173	9.606623	2.513331
71 H	3.319396	7.615407	4.045350
72 H	4.631364	4.070366	4.057330
73 H	4.614938	4.488757	2.323783
74 H	3.377043	3.393415	2.980433
75 H	2.795902	4.978623	5.623116
76 H	1.548101	4.300522	4.541620
77 H	1.515354	6.036203	4.965743
78 H	4.602654	6.544435	4.676621

Transition state for quinuclidine activation of diisopropylamine palladium anhydride κ² anhydride palladium anhydride **TS-15**



Bonding energy	*Internal energy*	*Entropy*	*Gibbs energy*
-9738.55	455.341	264.938	-9387.28

Atom	X	Y	Z
1 Pd	0.753697	-1.309310	0.617122
2 H	-0.512689	-2.943500	6.143413
3 H	-0.463934	-1.461249	5.145153
4 H	0.404790	2.417705	-4.961579
5 H	1.766493	4.334679	-2.905427
6 H	2.456173	3.829449	-4.471424
7 H	3.378102	3.587768	-2.957973
8 H	1.012832	-2.428559	5.377432
9 N	1.633779	-1.762011	-1.322418
10 C	3.098771	-2.128217	-1.179214
11 C	3.825360	-0.986201	-0.448282

12 C	3.803995	-2.434655	-2.515910
13 C	0.696027	-2.734901	-2.037198
14 C	0.679449	-2.542897	-3.565611
15 C	0.924285	-4.186871	-1.599214
16 H	1.568016	-0.860850	-1.814982
17 C	1.735285	2.172071	-3.255389
18 C	0.329346	2.163945	-3.893632
19 C	2.377120	3.569901	-3.405956
20 O	0.690766	0.973653	-1.438943
21 H	2.766208	1.363490	-5.007861
22 H	-0.322158	2.906027	-3.412721
23 C	1.706735	1.800633	-1.738306
24 C	0.420836	0.630153	0.202525
25 H	-2.385806	-2.359974	3.705714
26 H	3.122453	-3.026377	-0.546576
27 H	4.879274	-1.258136	-0.300370
28 H	3.374556	-0.788209	0.532588
29 H	3.783851	-0.053992	-1.026545
30 H	4.868855	-2.624742	-2.319491
31 H	3.732946	-1.578737	-3.200237
32 H	3.396356	-3.319476	-3.014873
33 H	-0.297770	-2.441780	-1.678591
34 H	1.614040	-2.850628	-4.045430
35 H	0.485239	-1.492057	-3.822068
36 H	-0.137052	-3.144921	-3.991176
37 H	1.874236	-4.588745	-1.974475
38 H	0.907072	-4.272712	-0.505093
39 H	0.114723	-4.809345	-2.005623
40 H	2.177393	0.112885	-3.892875
41 O	-0.096002	-1.375235	2.598421
42 C	0.127862	-2.642296	2.739506
43 C	-0.436650	-3.327679	3.995791
44 C	0.125886	-4.757459	4.130566
45 C	-1.981242	-3.374130	3.821508
46 C	-0.077326	-2.483036	5.244015
47 O	0.747750	-3.297162	1.838102
48 H	-0.126593	-5.363966	3.251148
49 H	-2.442921	-3.840391	4.704782
50 H	3.623078	1.069646	-3.470833
51 C	2.632920	1.109932	-3.945536
52 H	-2.256016	-3.964880	2.935463

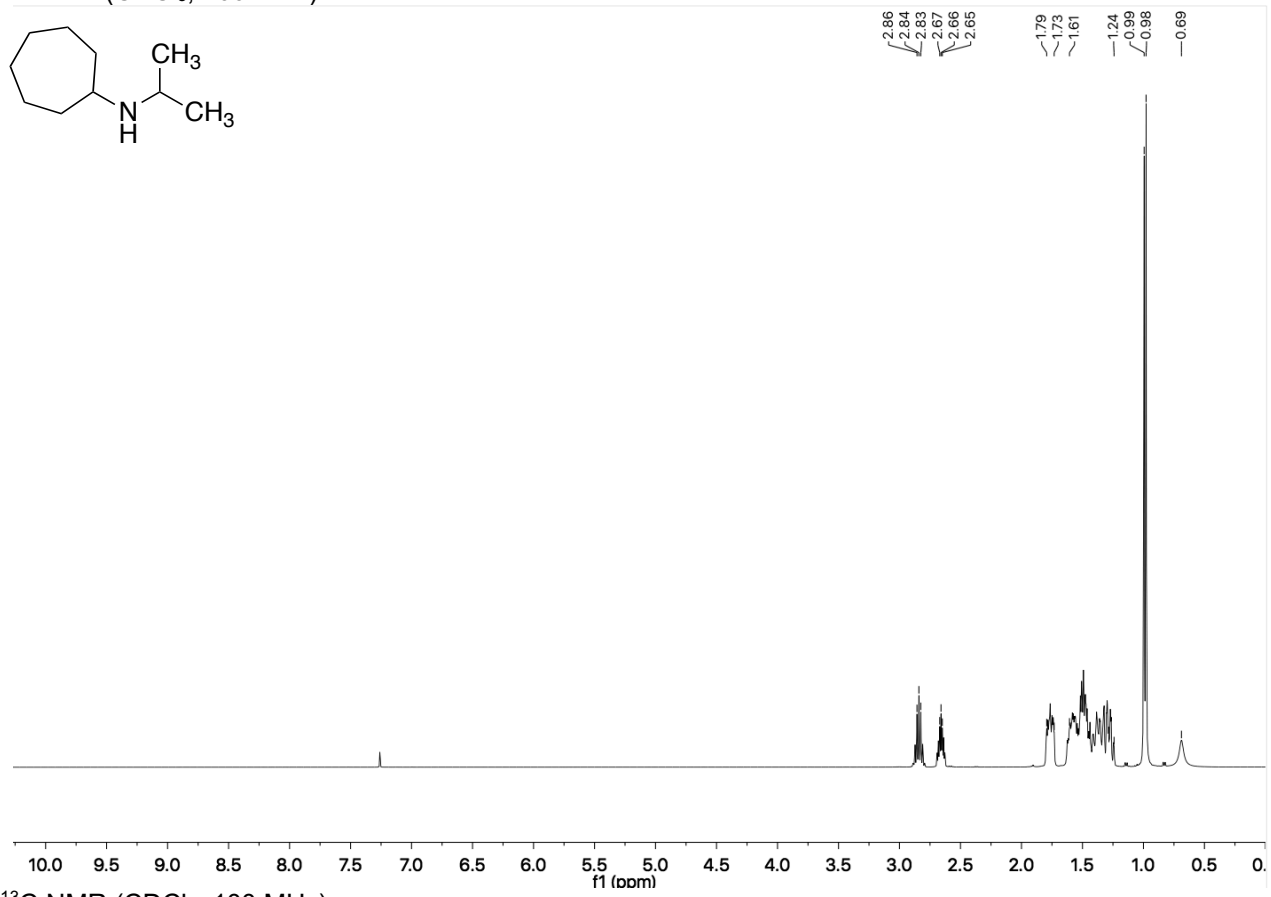
53 O	2.581845	2.175645	-0.965511
54 O	0.545908	1.542391	0.964225
55 H	-0.147542	1.180343	-3.803292
56 H	-0.296516	-5.238665	5.025155
57 H	1.220272	-4.740279	4.227229
58 N	-1.697738	0.624787	-0.217092
59 C	-2.165760	-0.384249	-1.205761
60 C	-2.001542	1.996639	-0.720867
61 C	-3.674071	-0.149350	-1.551043
62 C	-4.250584	0.875262	-0.541432
63 C	-3.545220	2.236596	-0.757397
64 C	-2.386411	0.409059	1.091746
65 C	-3.936913	0.391651	0.894618
66 H	-2.008782	-1.371878	-0.753666
67 H	-1.520641	-0.305469	-2.088854
68 H	-1.559101	2.071651	-1.717694
69 H	-1.481601	2.708429	-0.067083
70 H	-4.229864	-1.096850	-1.496390
71 H	-3.779657	0.238510	-2.575475
72 H	-3.849286	2.940639	0.032186
73 H	-3.837212	2.674685	-1.723308
74 H	-2.059864	1.219302	1.755883
75 H	-2.017209	-0.528694	1.517177
76 H	-4.424696	1.044659	1.632951
77 H	-4.331311	-0.625450	1.040920
78 H	-5.336232	0.978197	-0.683809

Appendix 2: NMR spectra

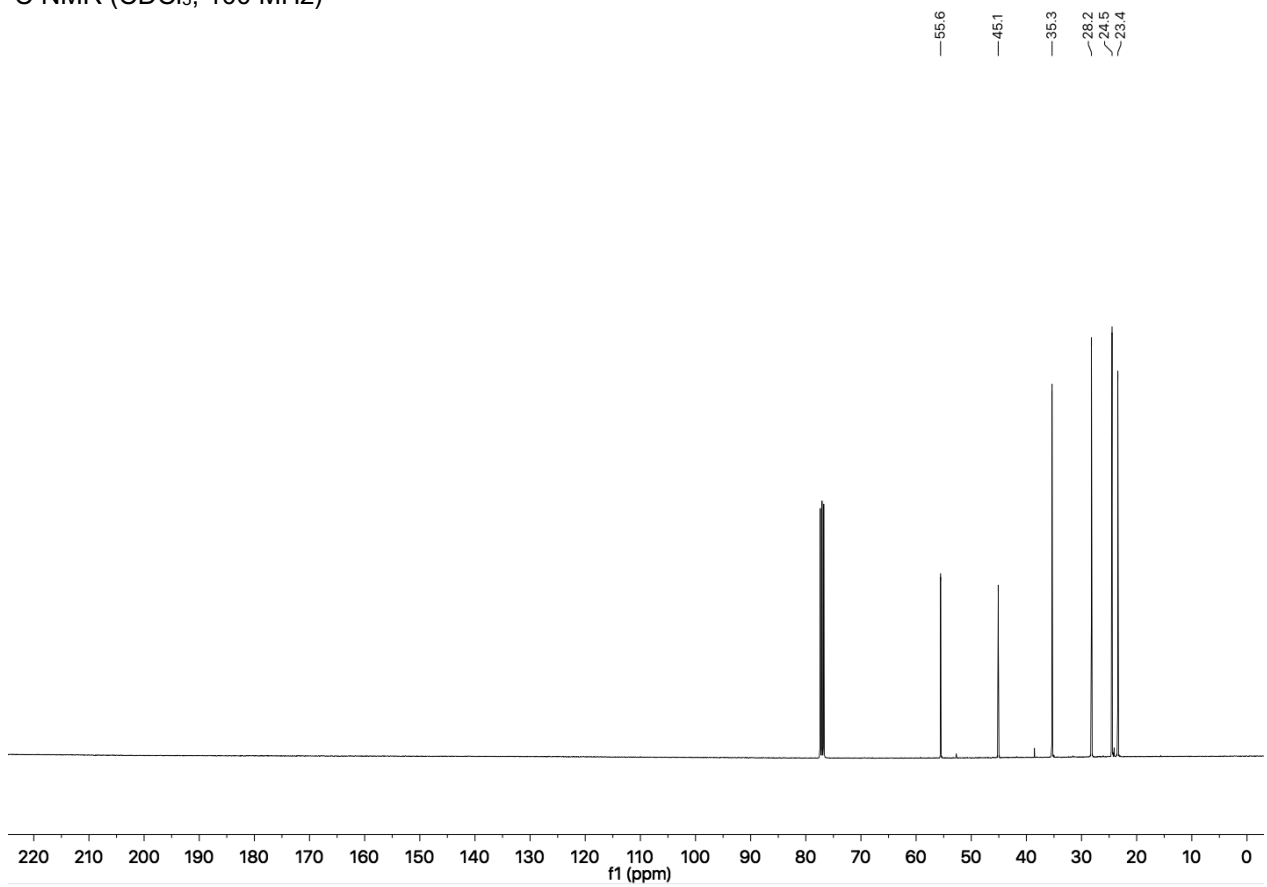
Carbonylation substrates

N-(isopropyl)cycloheptylamine (**337**)

^{1}H NMR ($CDCl_3$, 400 MHz)

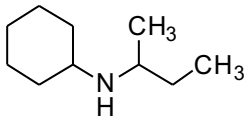


^{13}C NMR ($CDCl_3$, 100 MHz)

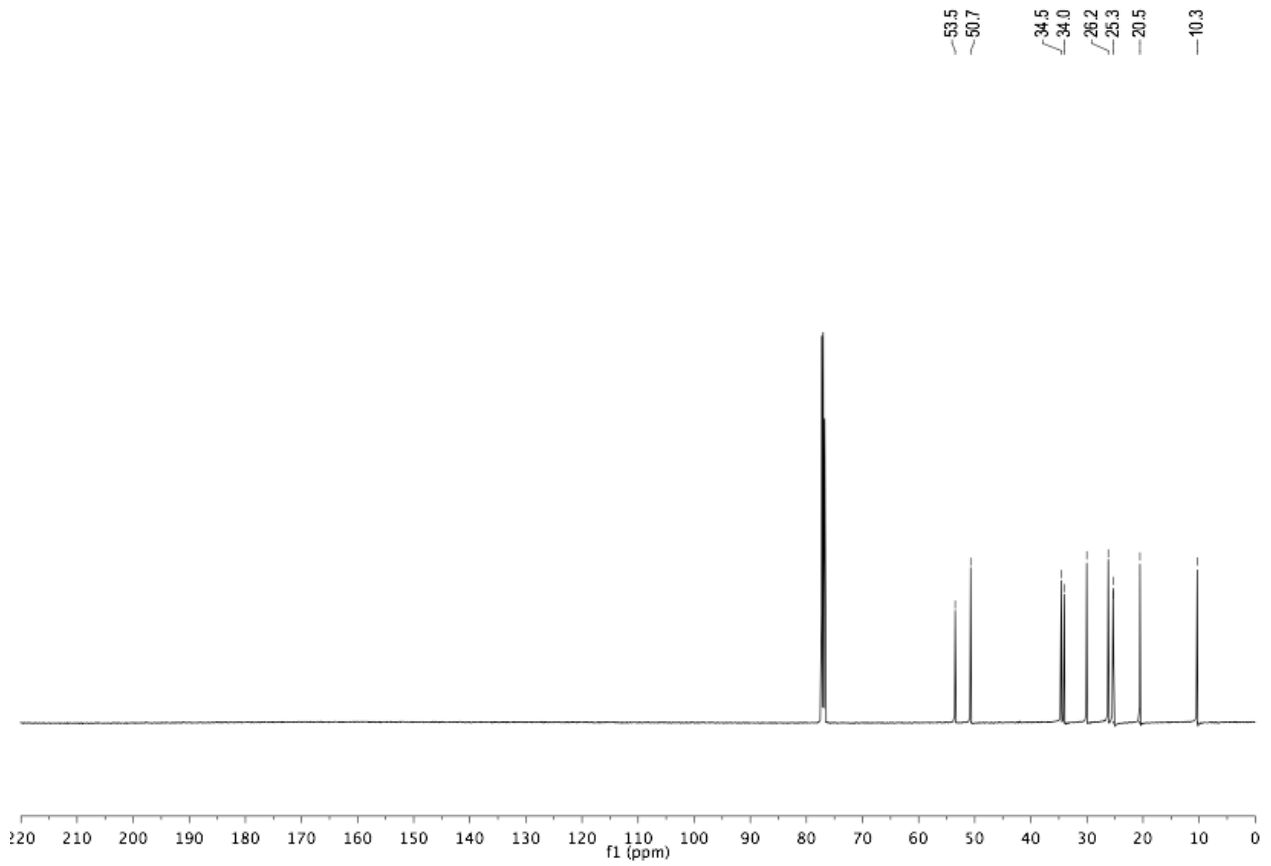


N-(sec-Butyl)cyclohexanamine (**282**)

^{1}H NMR ($CDCl_3$, 400 MHz)

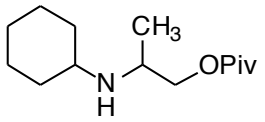


^{13}C NMR ($CDCl_3$, 100 MHz)

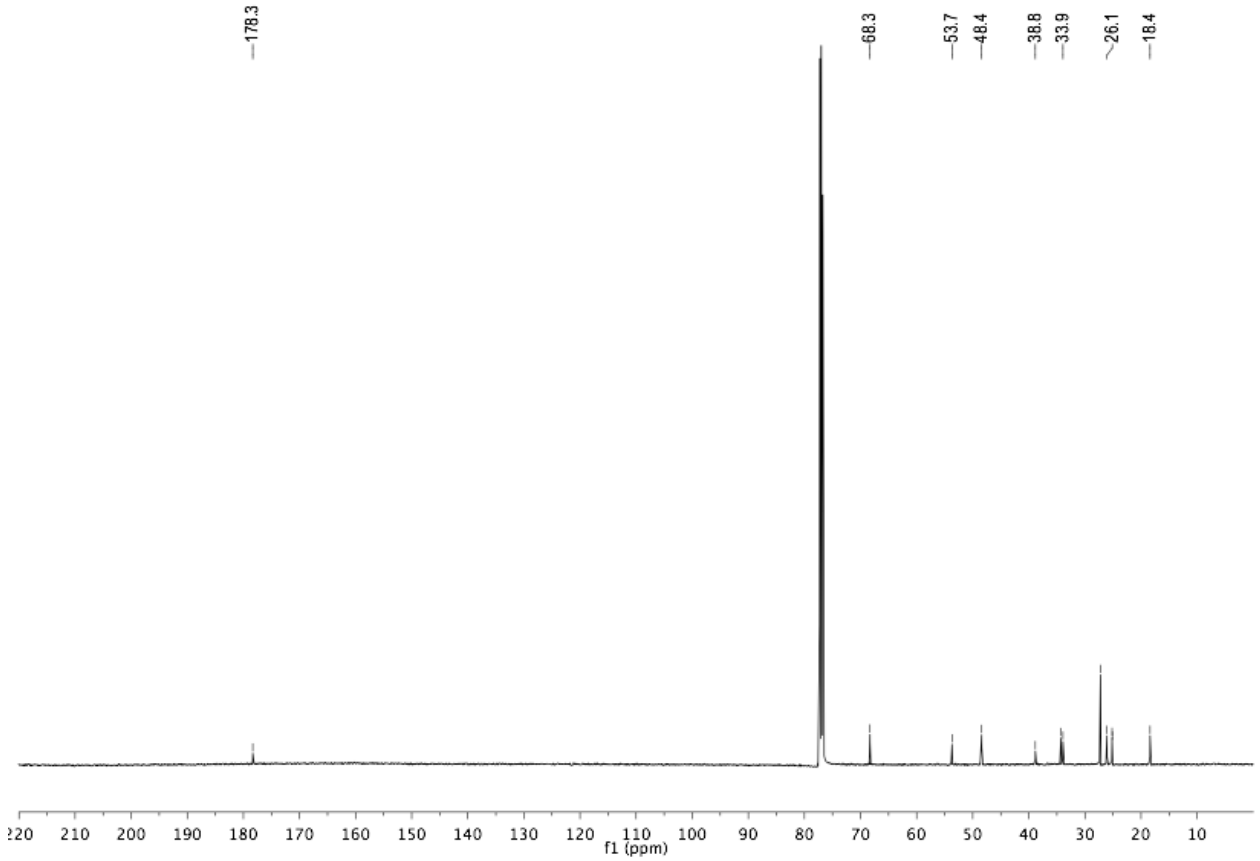


2-(Cyclohexylamino)propyl pivalate (**338**)

^{1}H NMR ($CDCl_3$, 400 MHz)

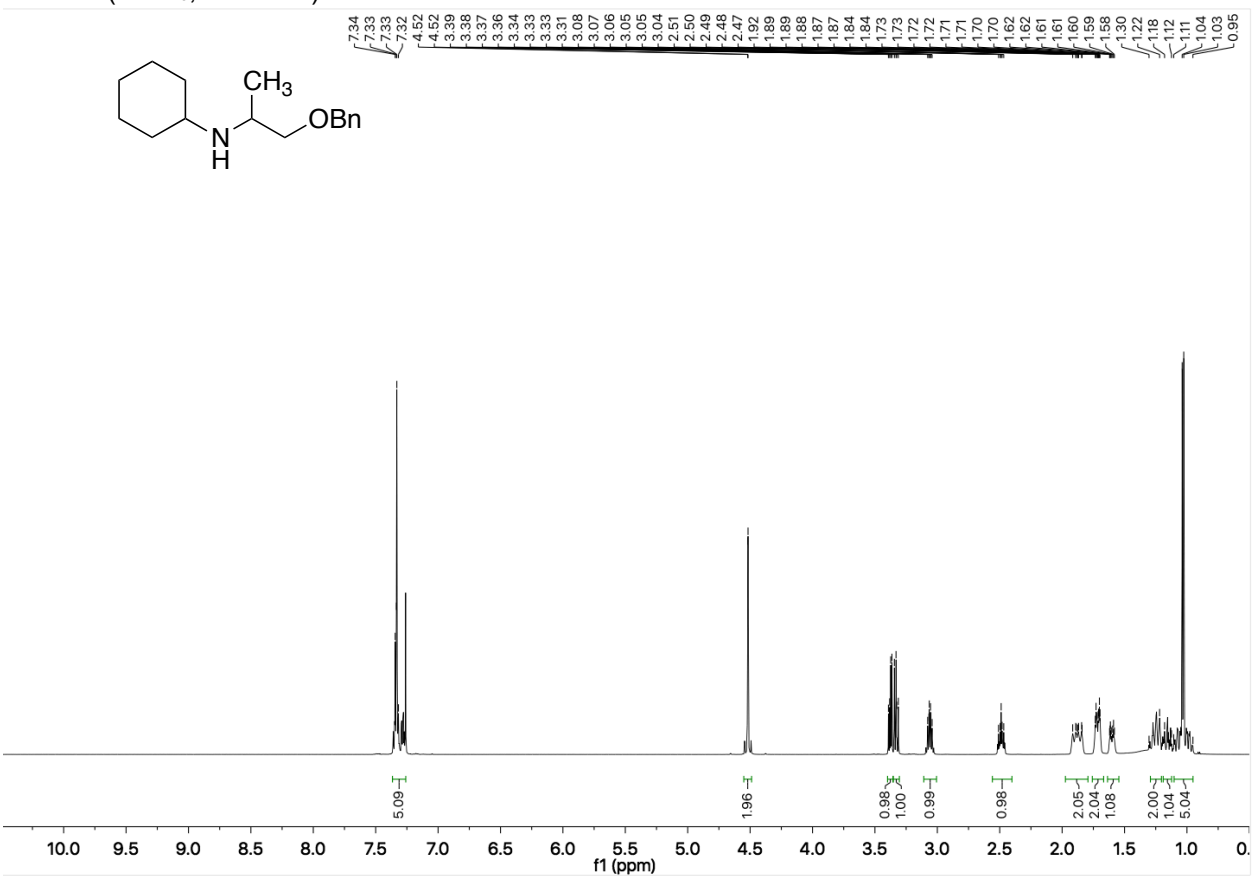


^{13}C NMR ($CDCl_3$, 100 MHz)

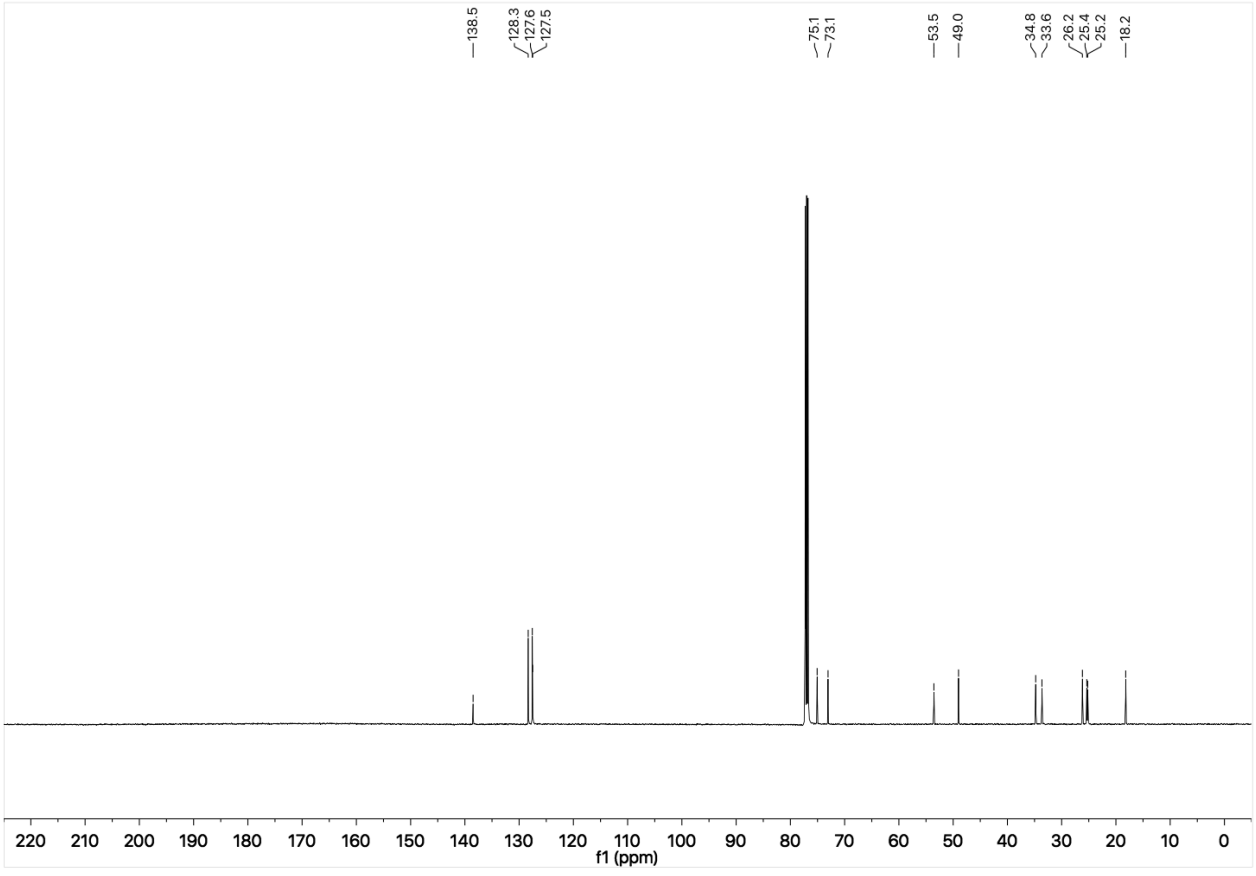


N-(1-(Benzyloxy)propan-2-yl)cyclohexanamine (**339**)

^{1}H NMR ($CDCl_3$, 400 MHz)

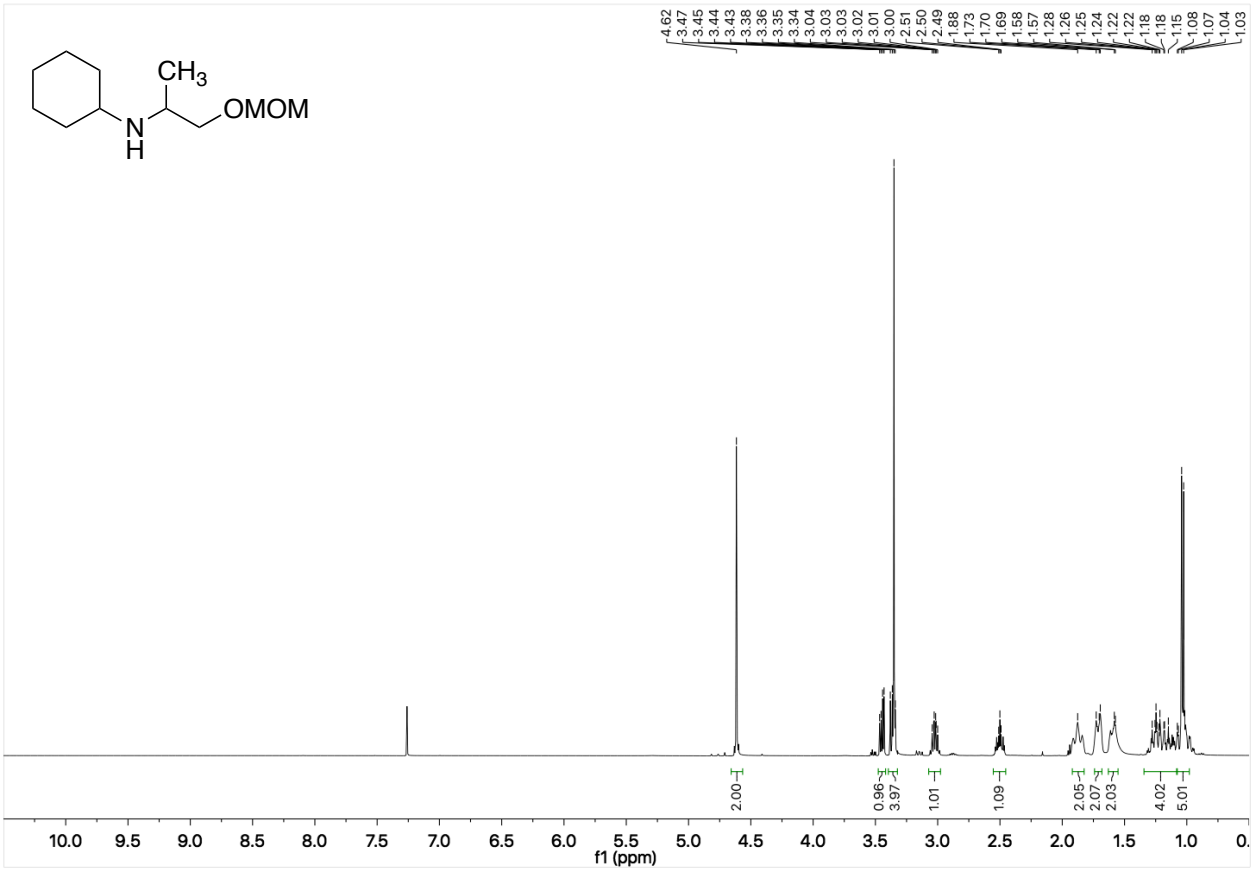


^{13}C NMR ($CDCl_3$, 100 MHz)

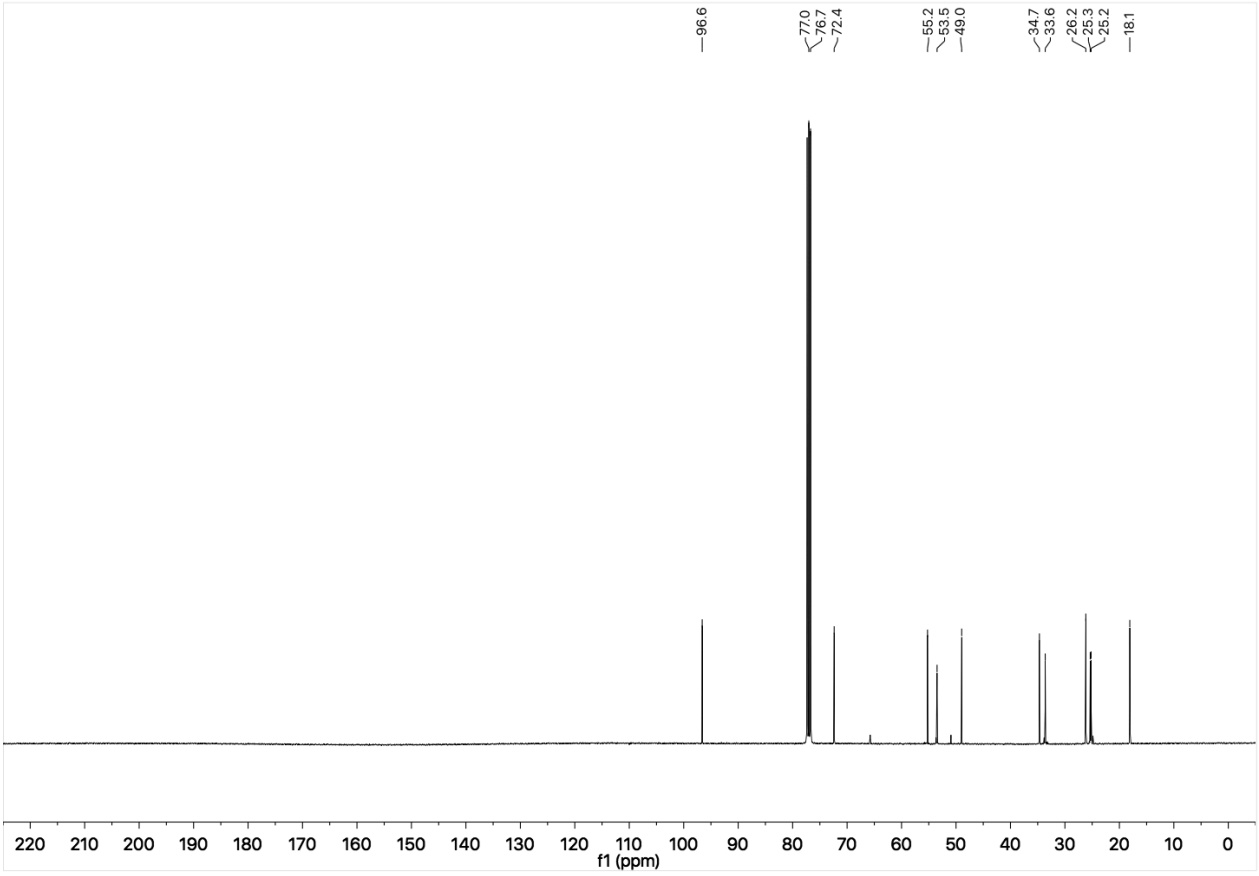


N-(1-(Methoxymethoxy)propan-2-yl)cyclohexanamine (**340**)

^{1}H NMR ($CDCl_3$, 400 MHz)

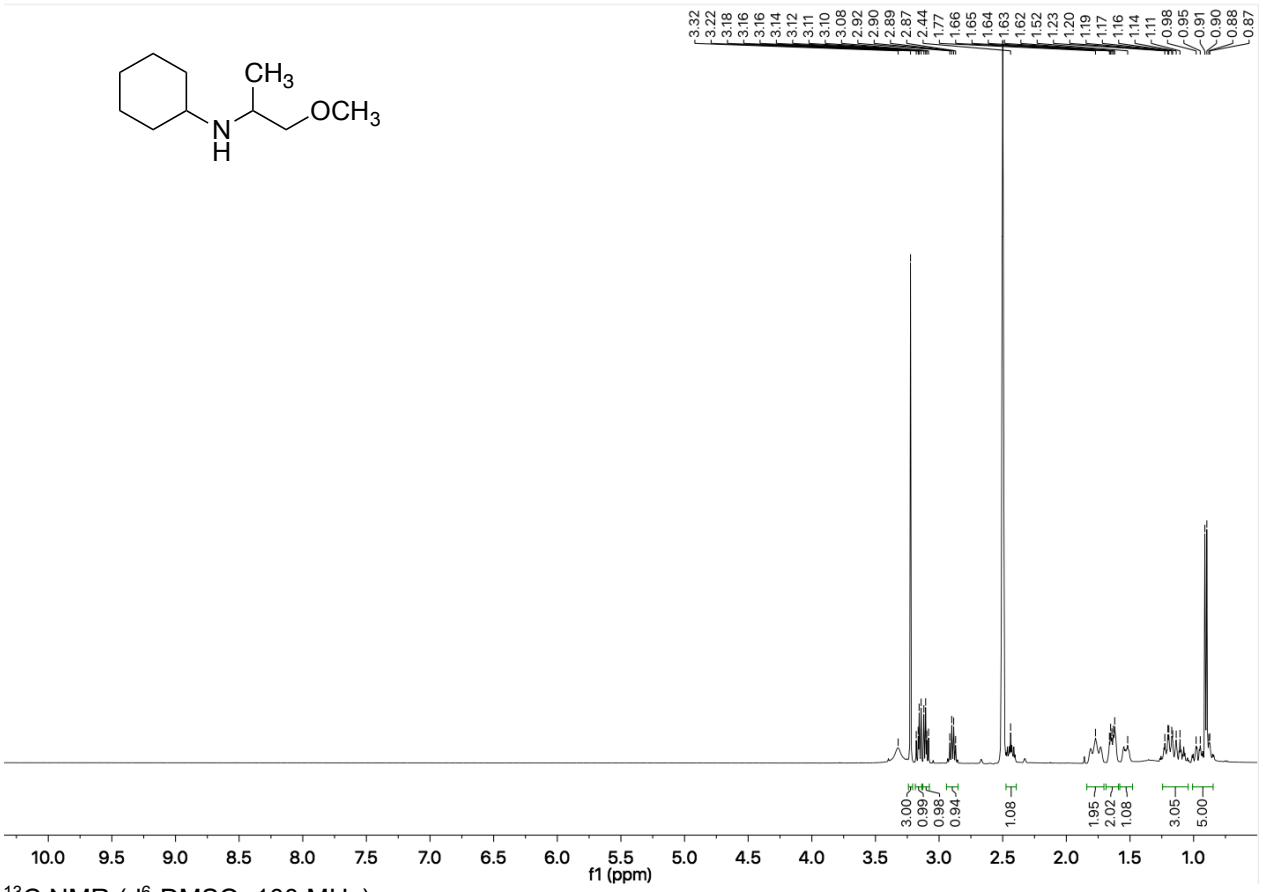


^{13}C NMR ($CDCl_3$, 100 MHz)

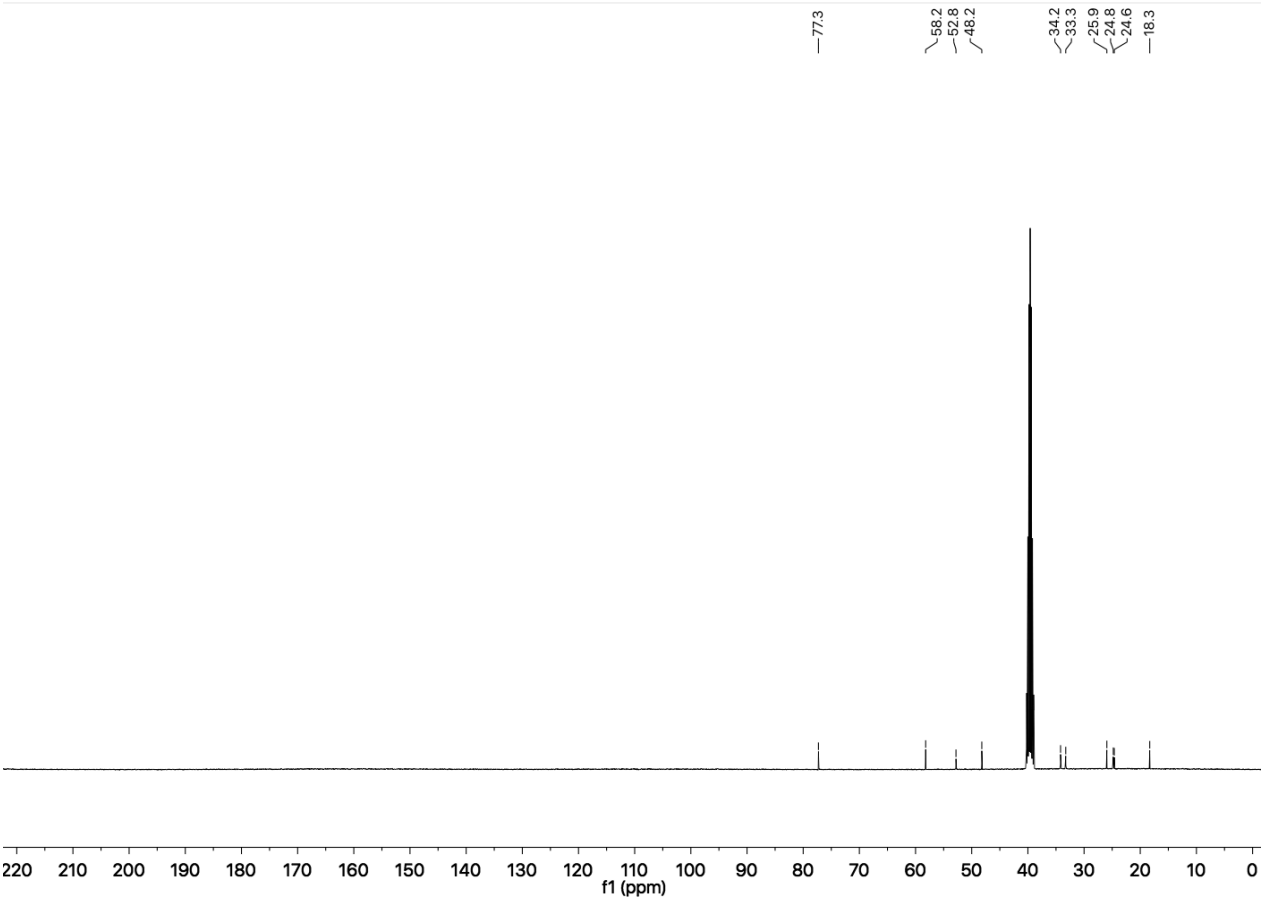


N-(1-Methoxypropan-2-yl)cyclohexanamine (**341**)

^{1}H NMR (d^{6}-DMSO, 400 MHz)

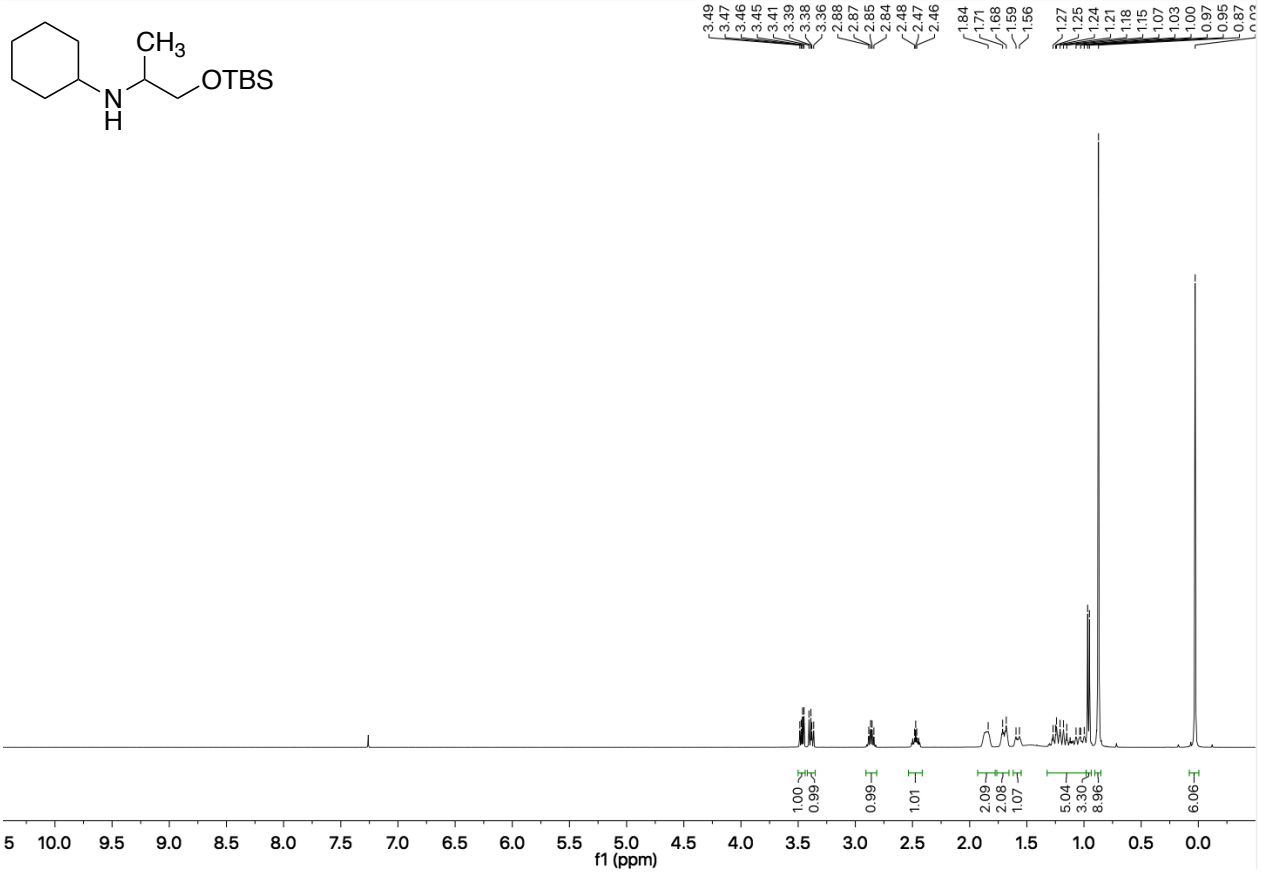


^{13}C NMR (d^{6}-DMSO, 100 MHz)

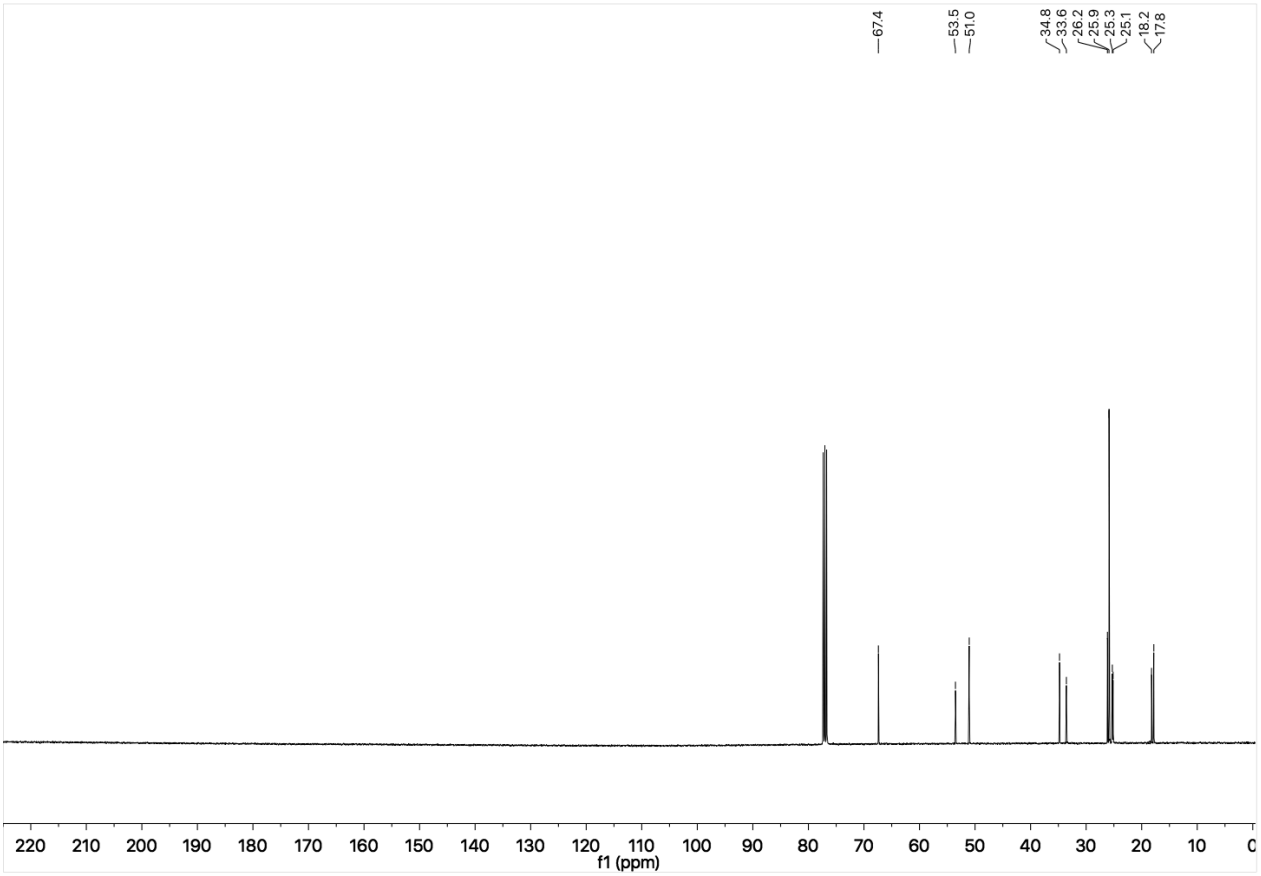


N-(1-((tert-Butyldimethylsilyl)oxy)propan-2-yl)cyclohexanamine (**342**)

^{1}H NMR ($CDCl_3$, 400 MHz)

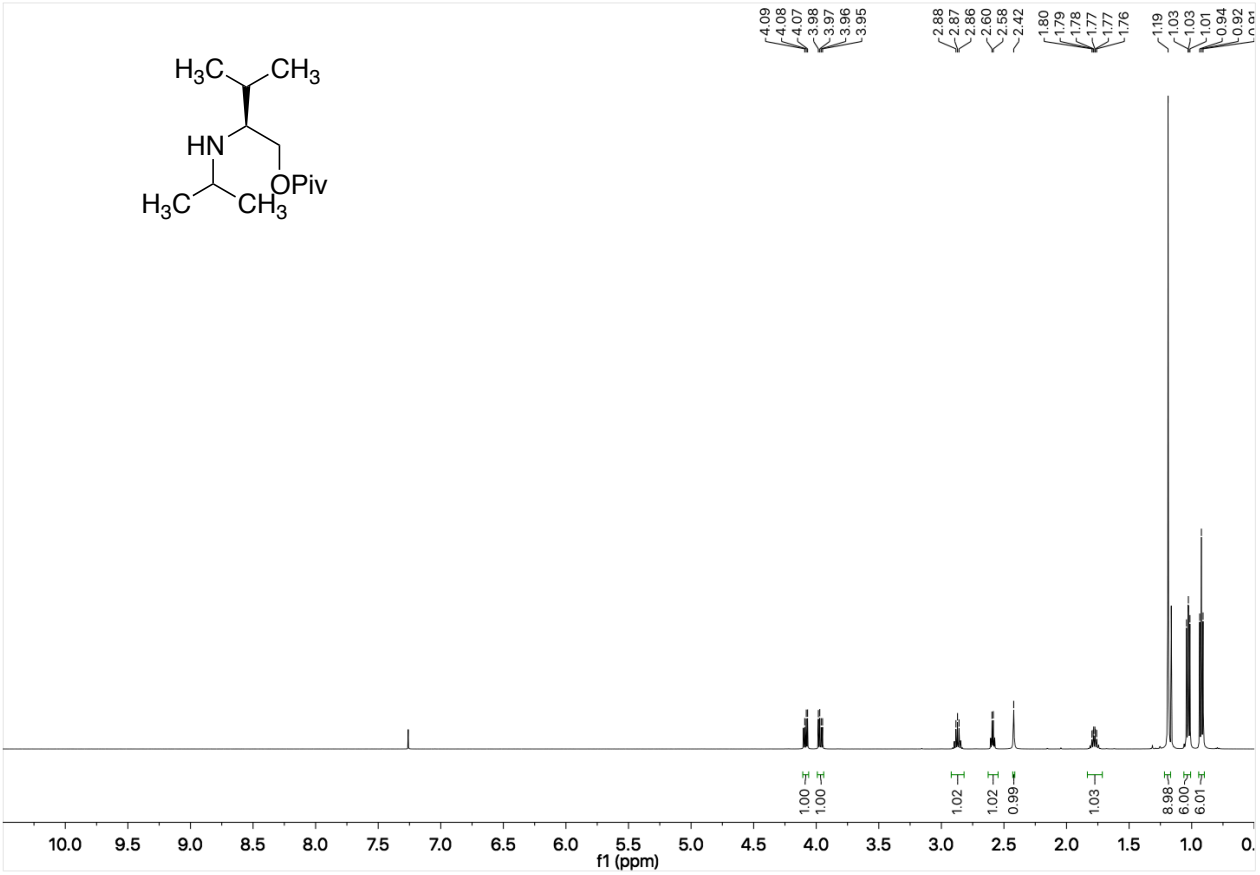


^{13}C NMR ($CDCl_3$, 100 MHz)

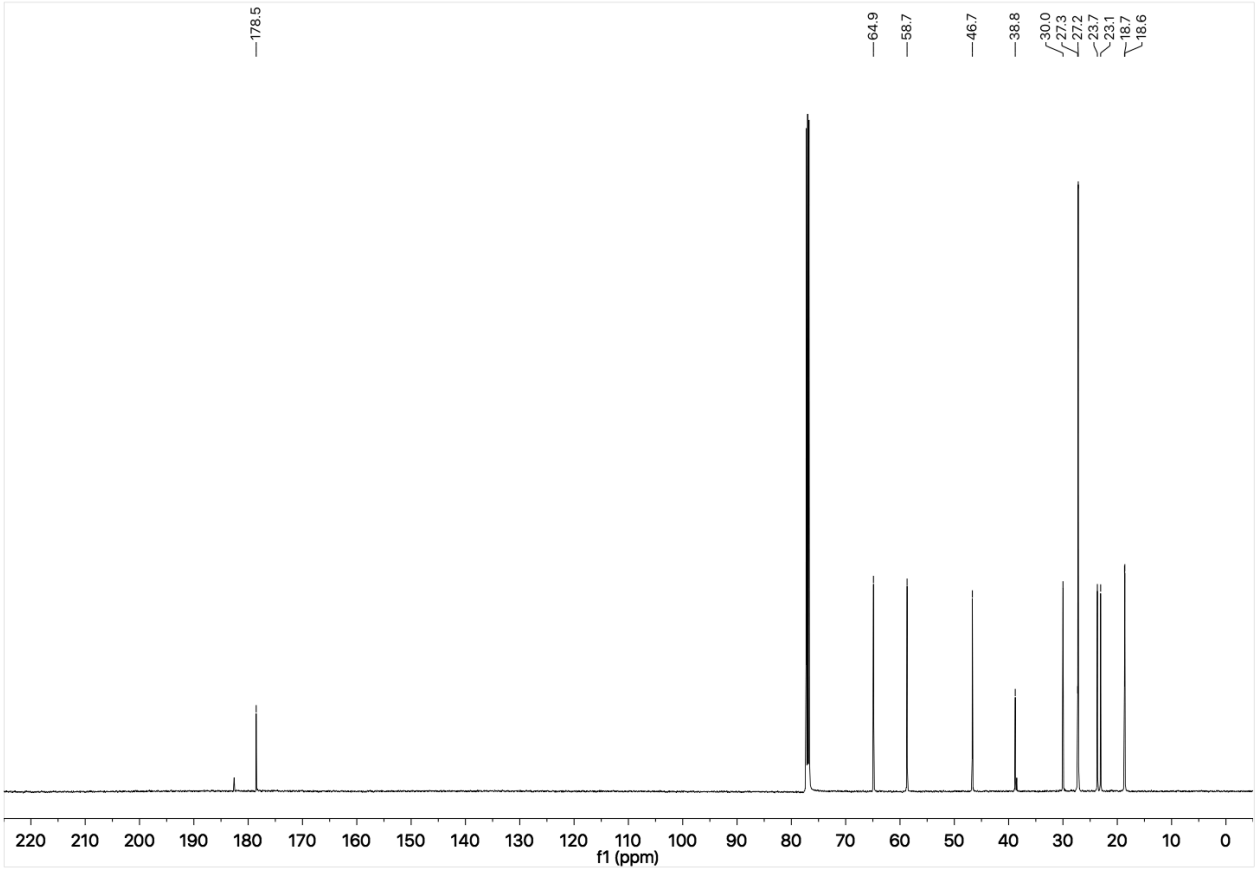


(*S*)-2-(Isopropylamino)-3-methylbutyl pivalate (**343**)

^{1}H NMR ($CDCl_3$, 400 MHz)

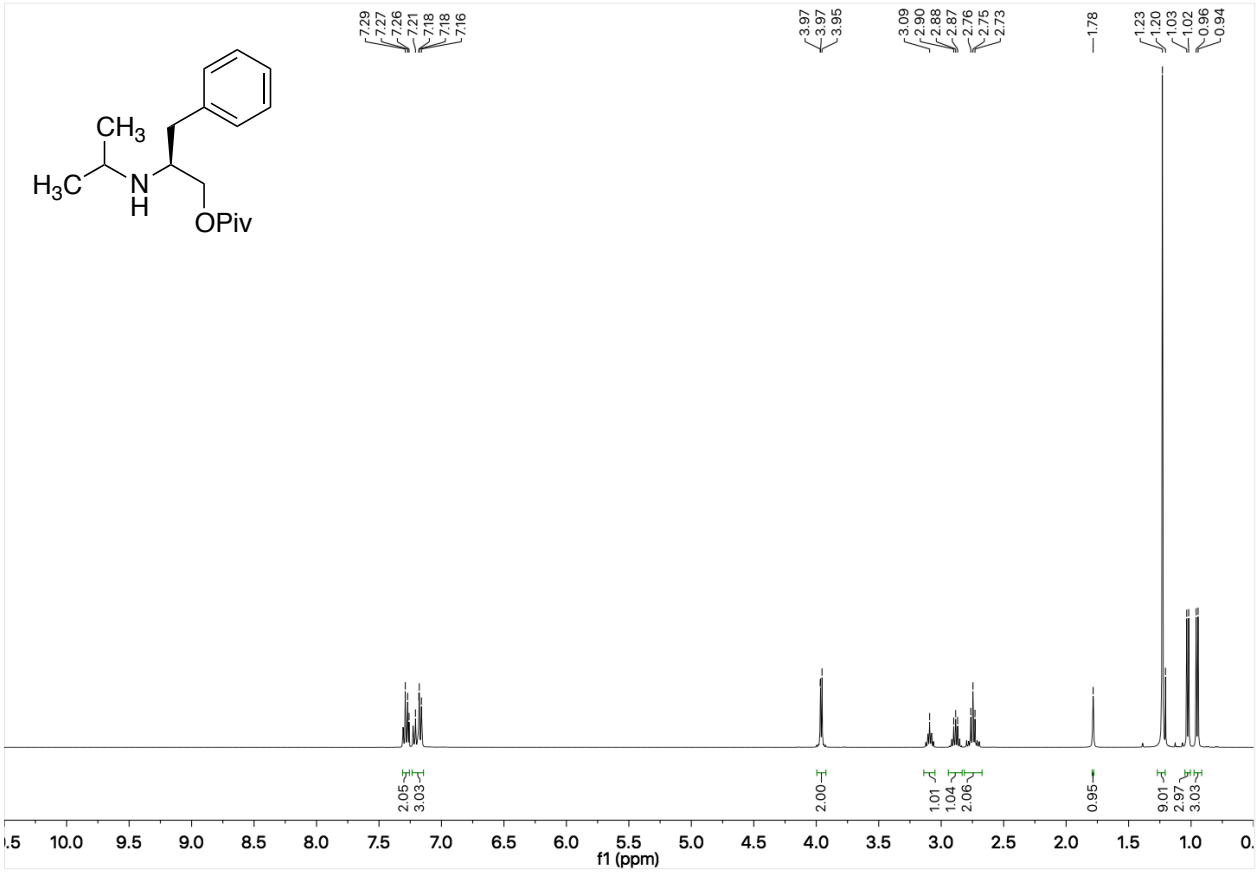


^{13}C NMR ($CDCl_3$, 100 MHz)

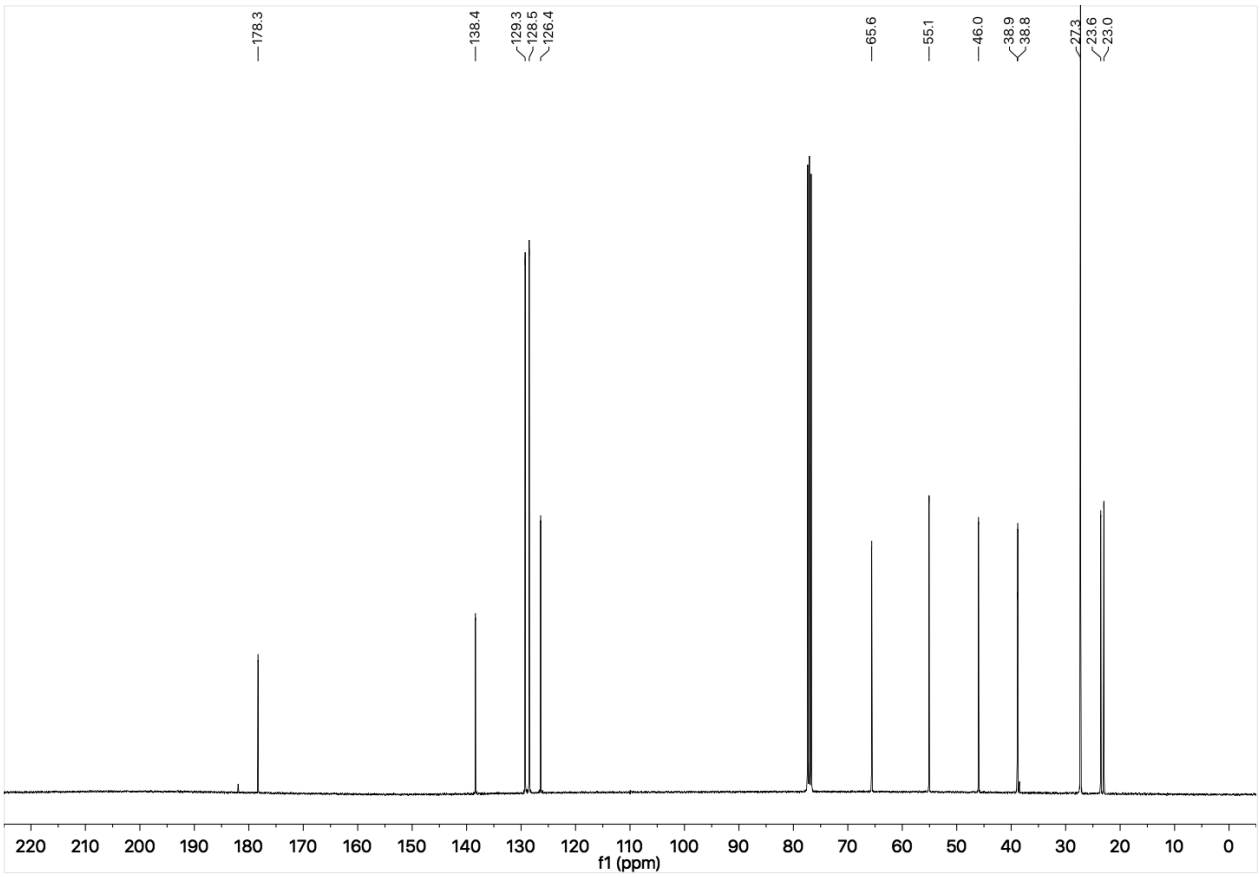


(S)-2-(Isopropylamino)-3-phenylpropyl pivalate (**263**)

^{1}H NMR ($CDCl_3$, 400 MHz)

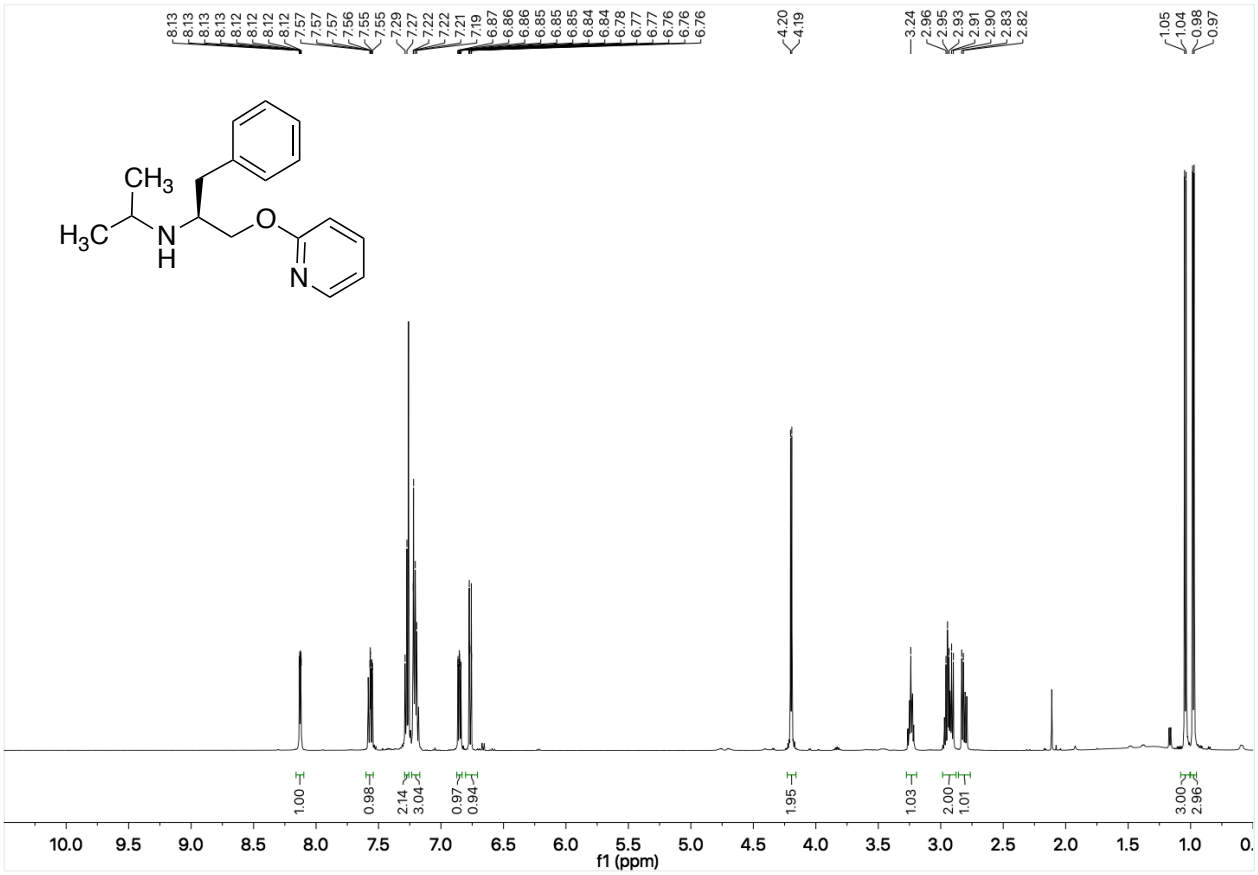


^{13}C NMR ($CDCl_3$, 100 MHz)

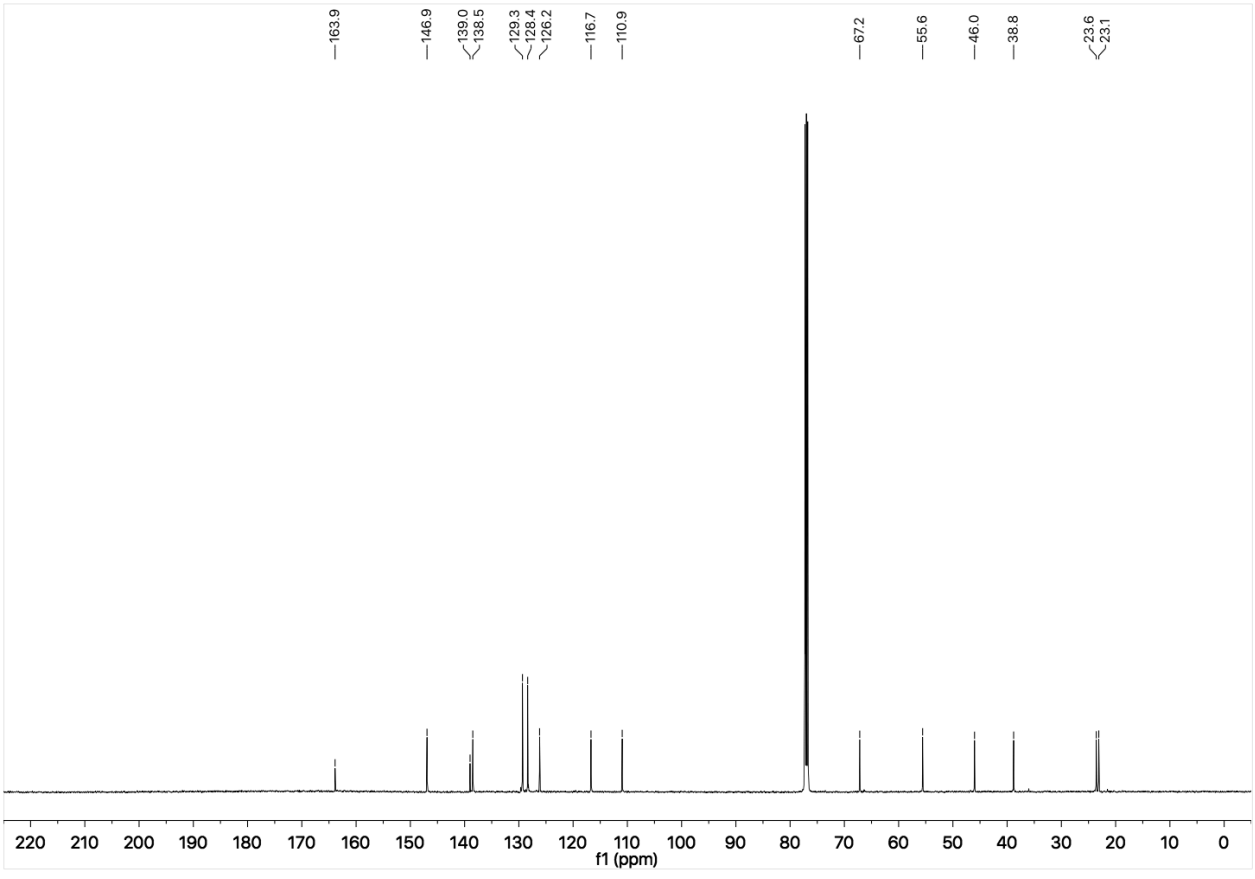


(S)-N-Isopropyl-1-phenyl-3-(pyridin-2-yloxy)propan-2-amine (**344**)

^{1}H NMR ($CDCl_3$, 400 MHz)

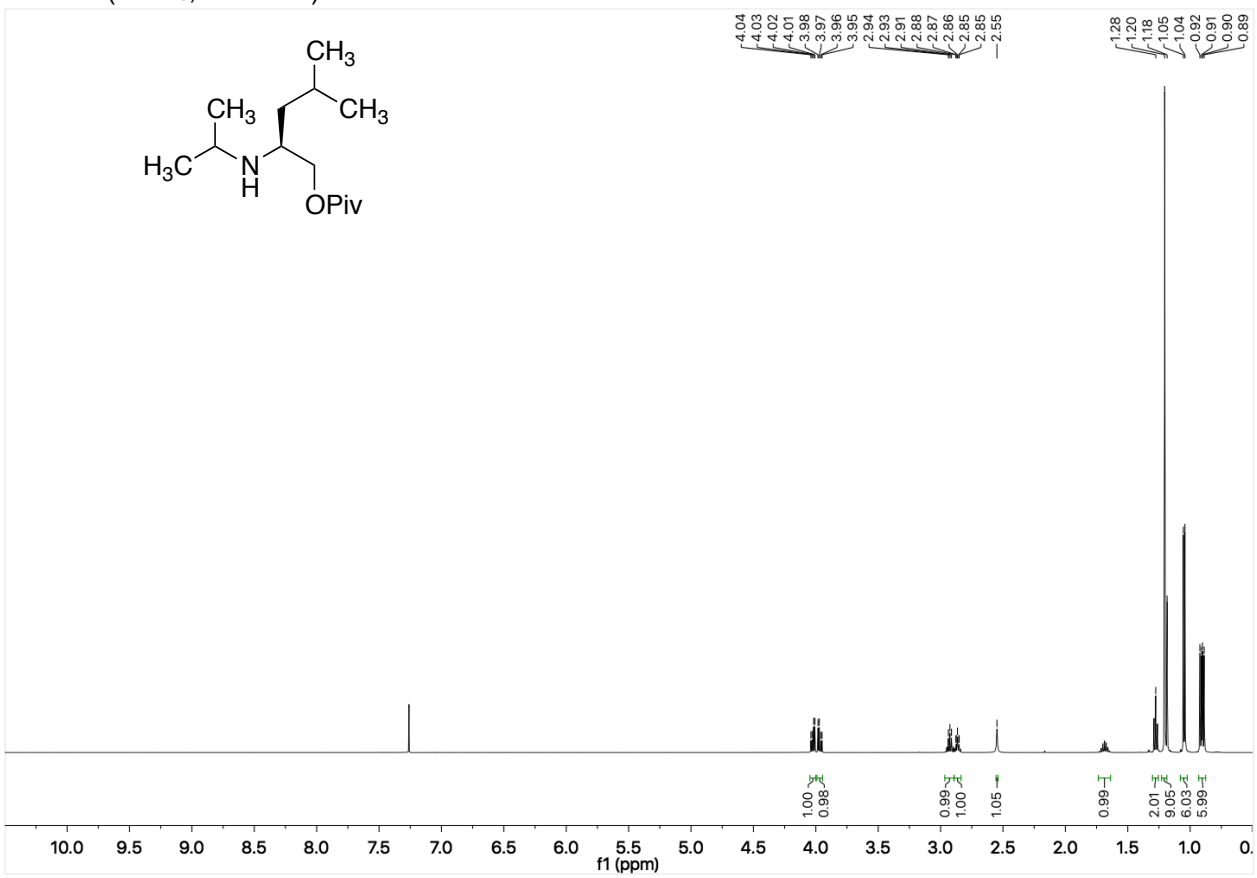


^{13}C NMR ($CDCl_3$, 100 MHz)

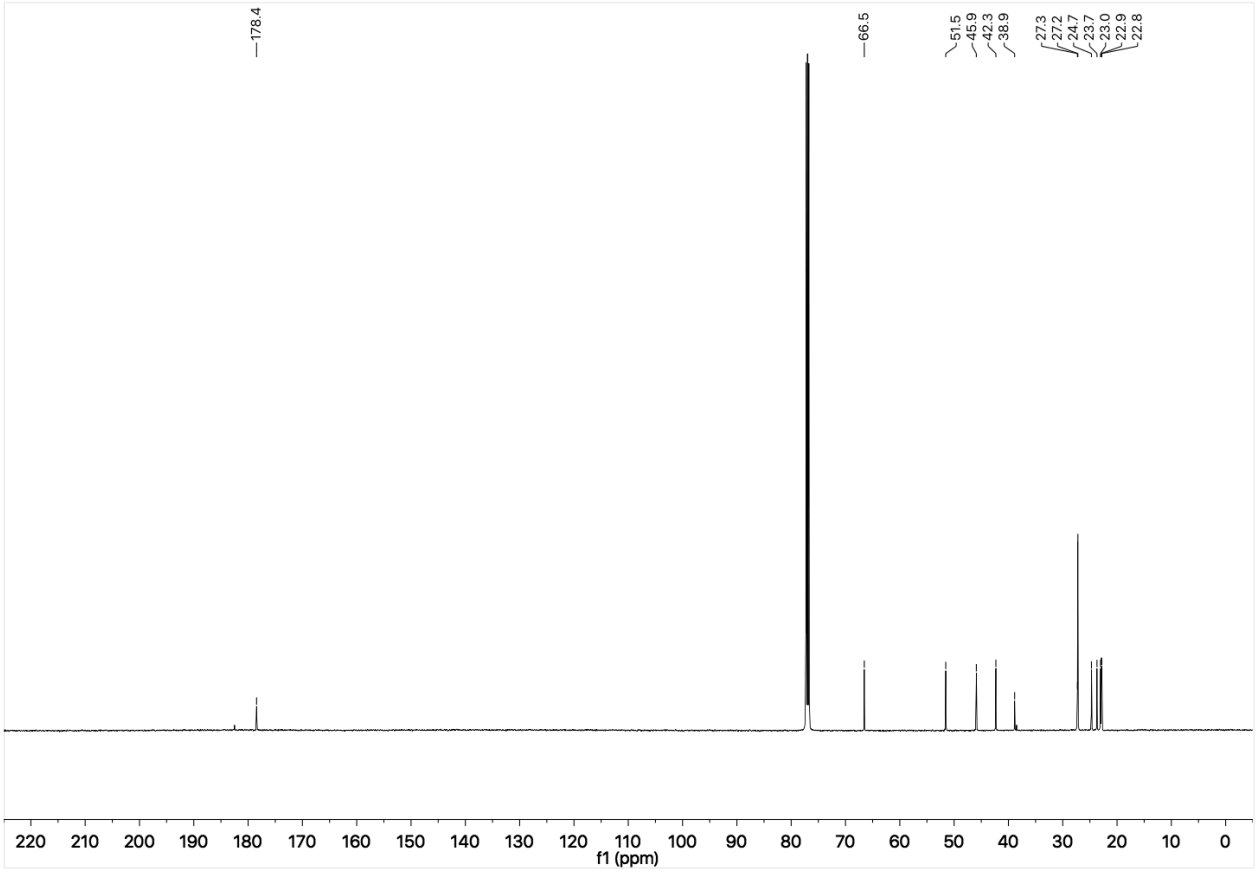


(S)-2-(Isopropylamino)-4-methylpentyl pivalate (**345**)

^{1}H NMR ($CDCl_3$, 400 MHz)

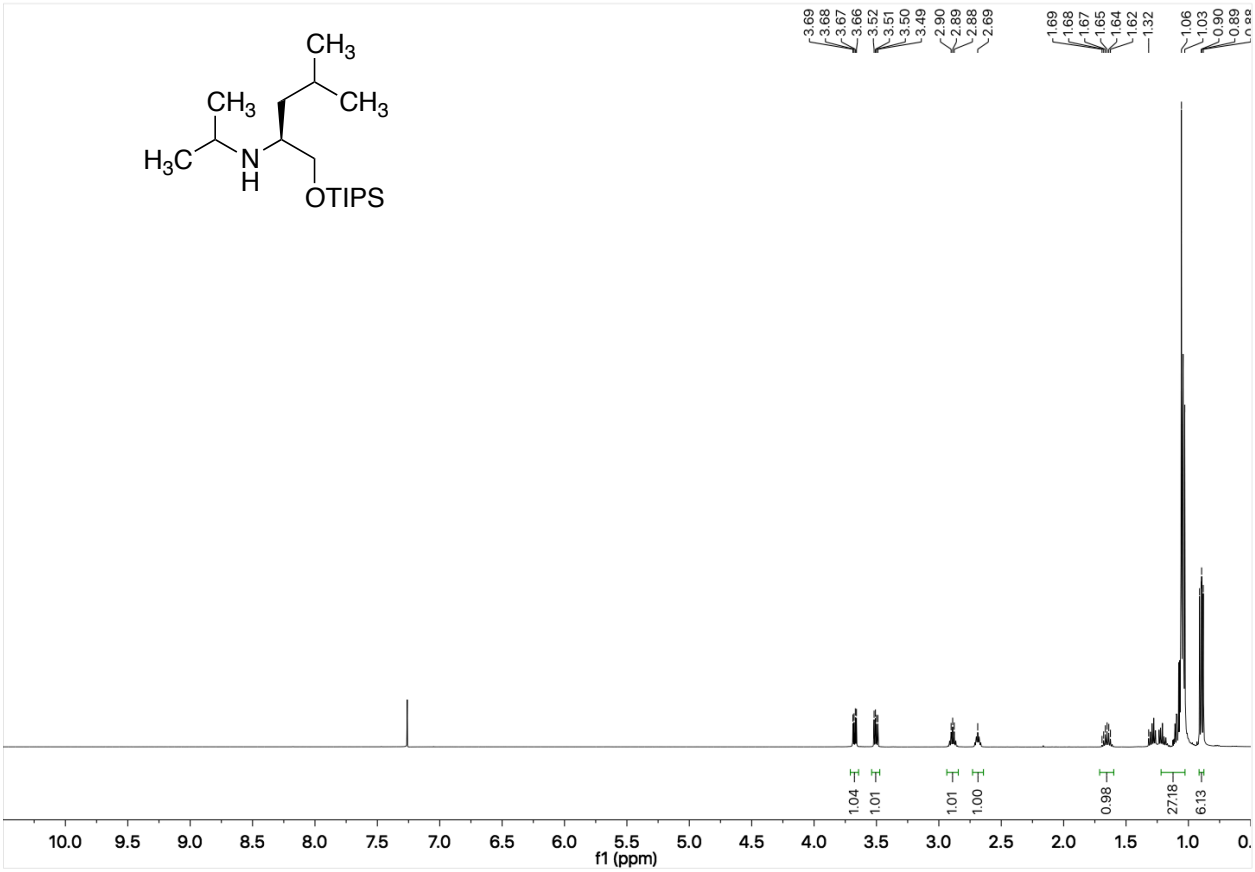


^{13}C NMR ($CDCl_3$, 100 MHz)

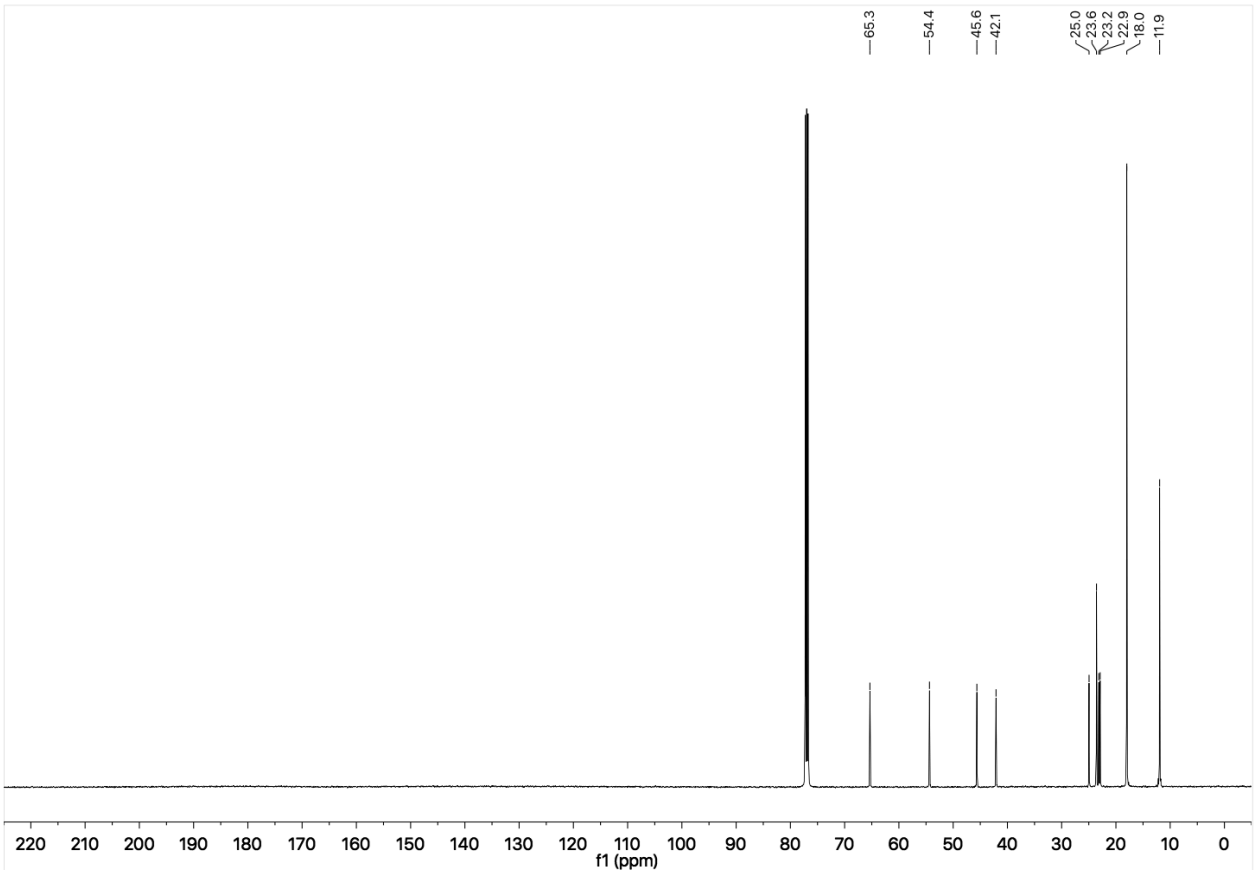


(S)-N-Isopropyl-4-methyl-1-((triisopropylsilyl)oxy)pentan-2-amine (**346**)

^{1}H NMR ($CDCl_3$, 400 MHz)

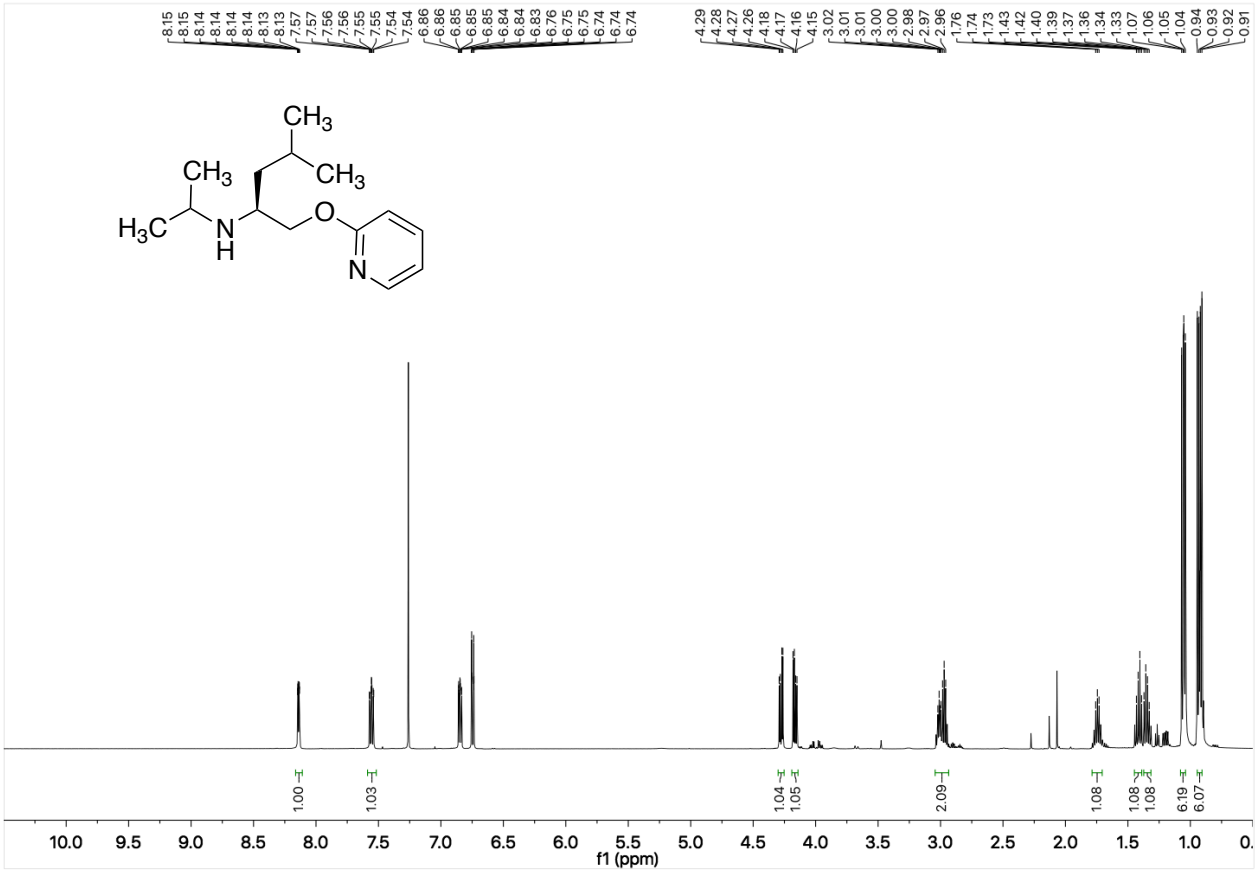


^{13}C NMR ($CDCl_3$, 100 MHz)

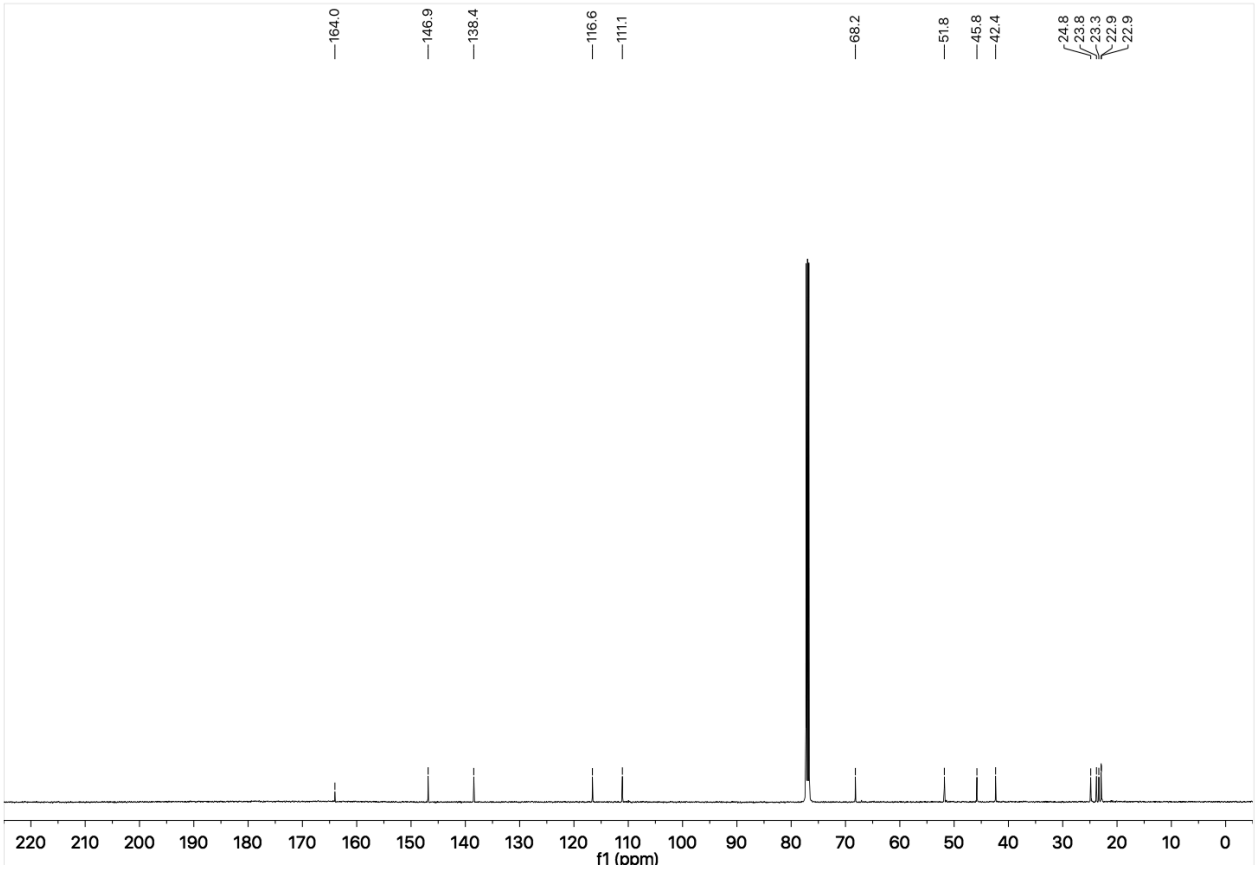


(S)-N-Isopropyl-4-methyl-1-(pyridin-2-yloxy)pentan-2-amine (**347**)

^{1}H NMR ($CDCl_3$, 400 MHz)

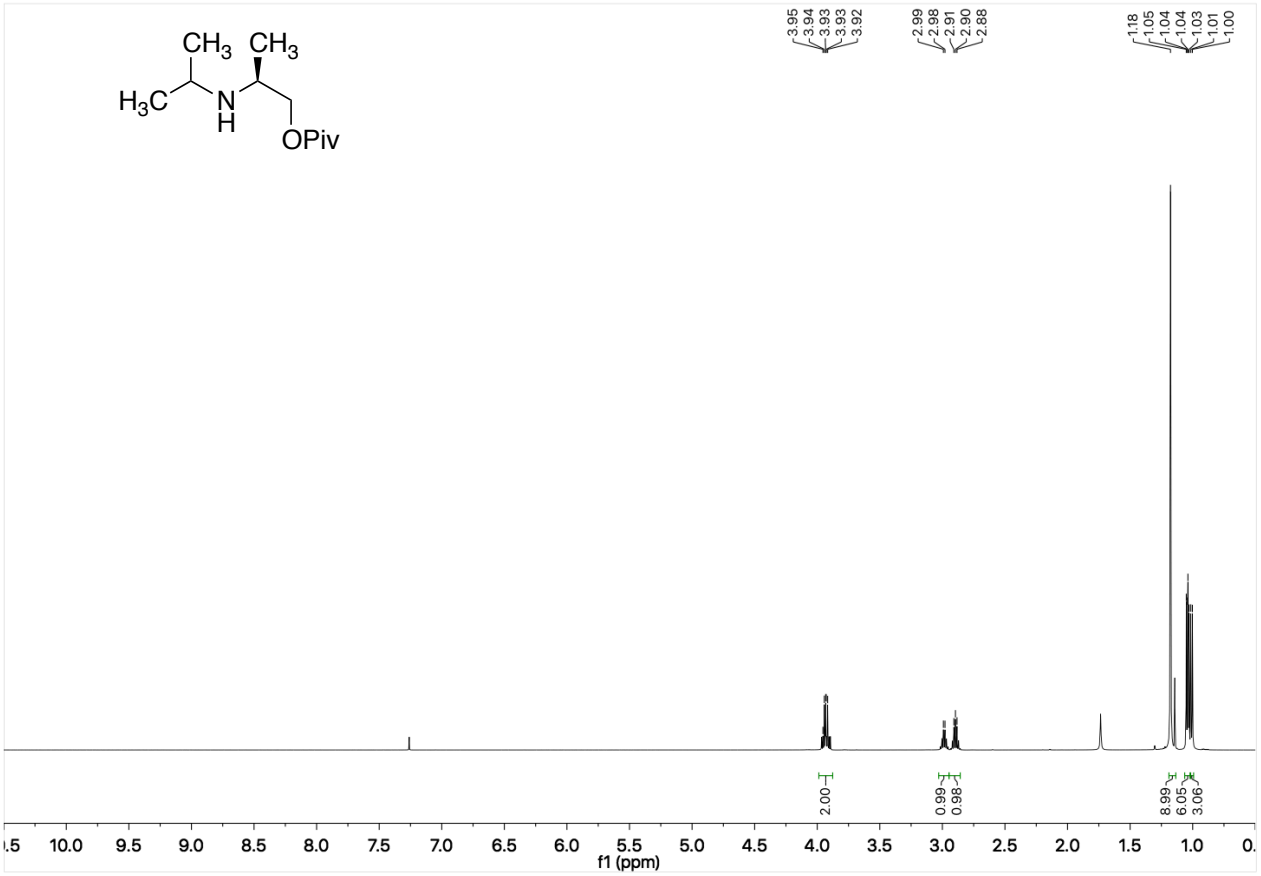


^{13}C NMR ($CDCl_3$, 100 MHz)

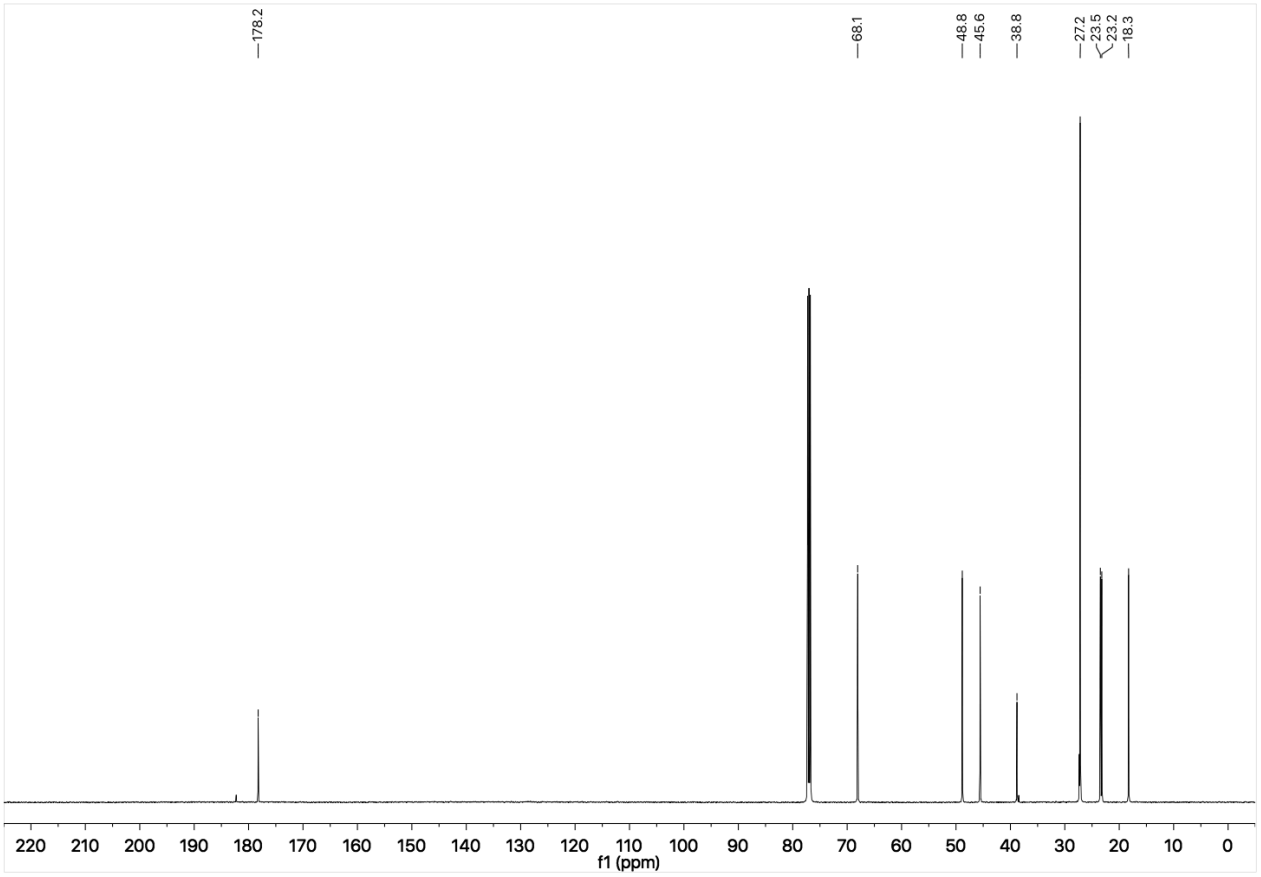


(S)-2-(Isopropylamino)propyl pivalate (**348**)

^{1}H NMR ($CDCl_3$, 400 MHz)

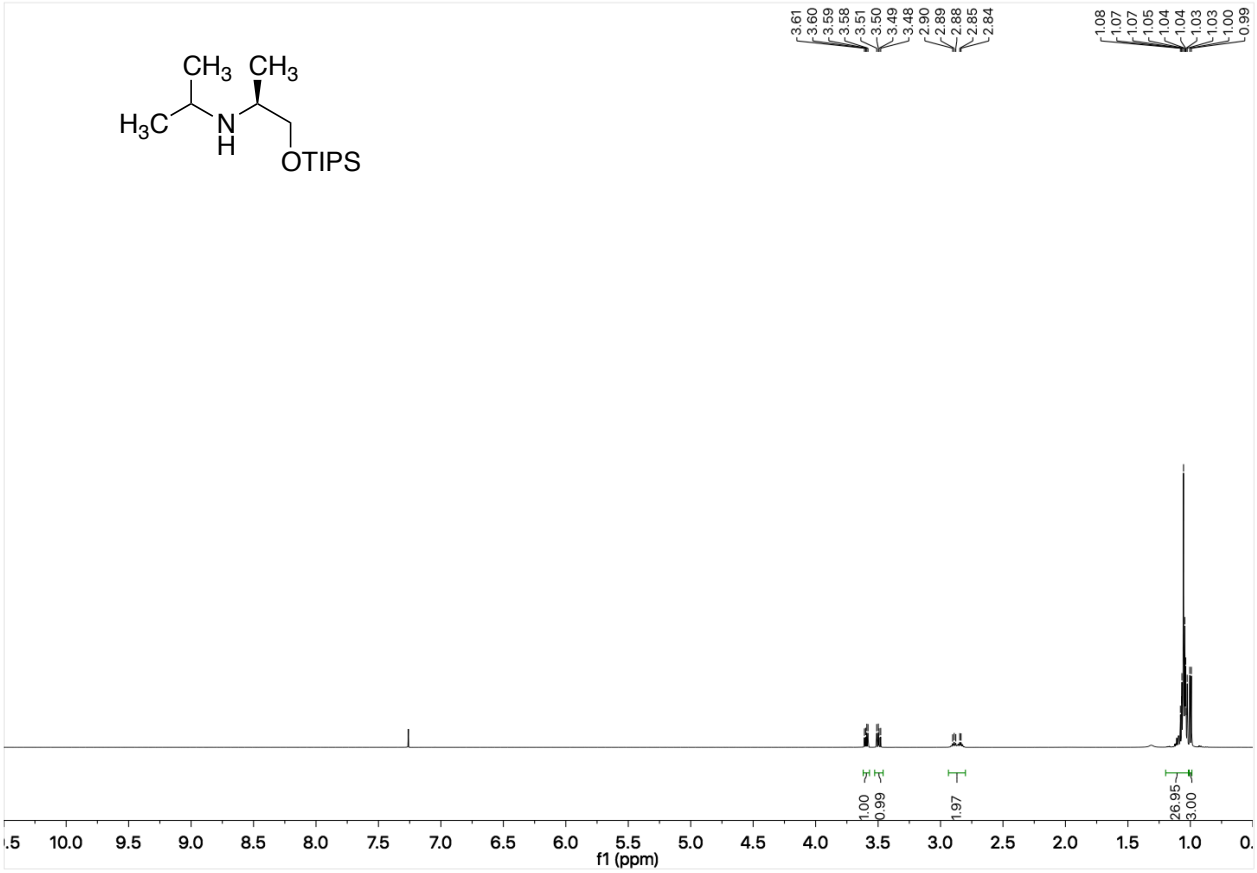


^{13}C NMR ($CDCl_3$, 100 MHz)

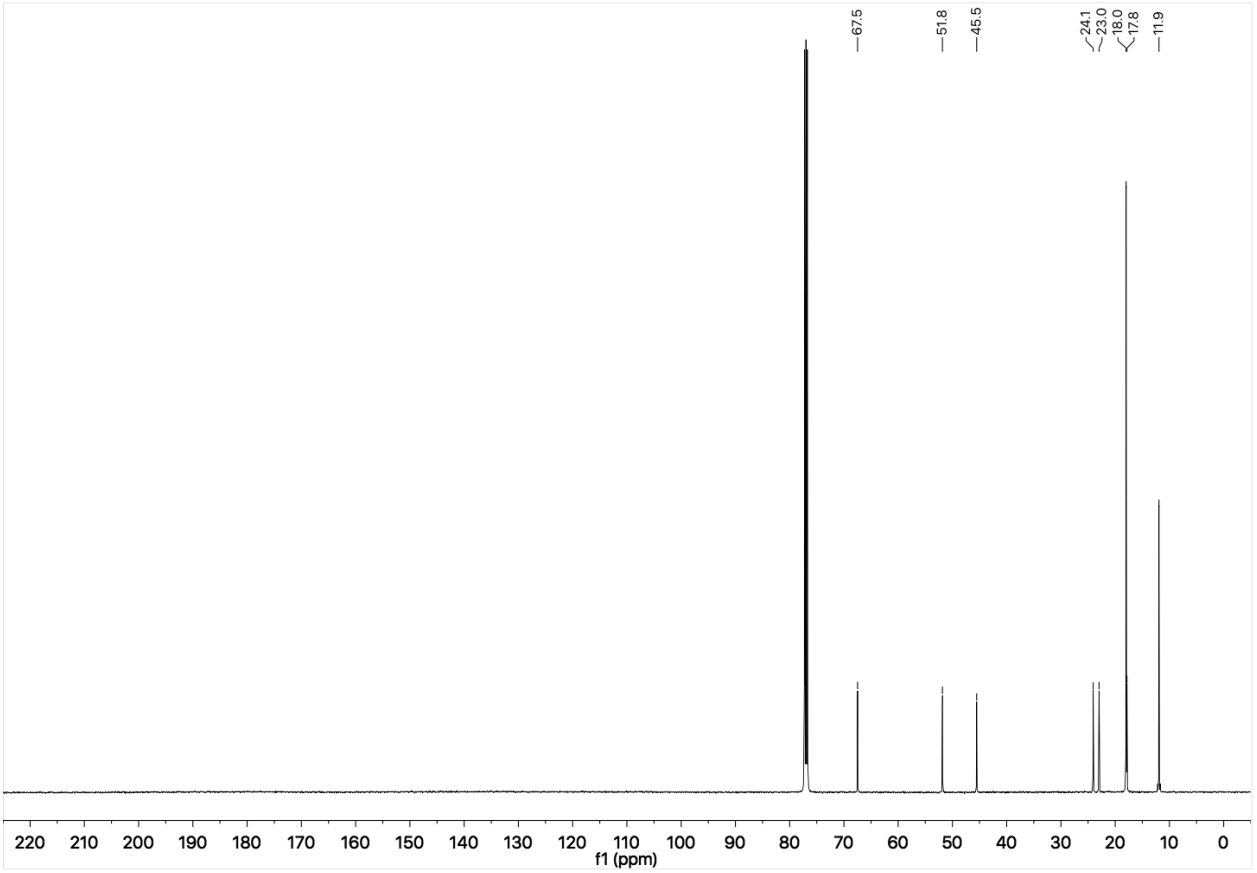


(S)-N-Isopropyl-1-((triisopropylsilyl)oxy)propan-2-amine (**349**)

^{1}H NMR ($CDCl_3$, 400 MHz)

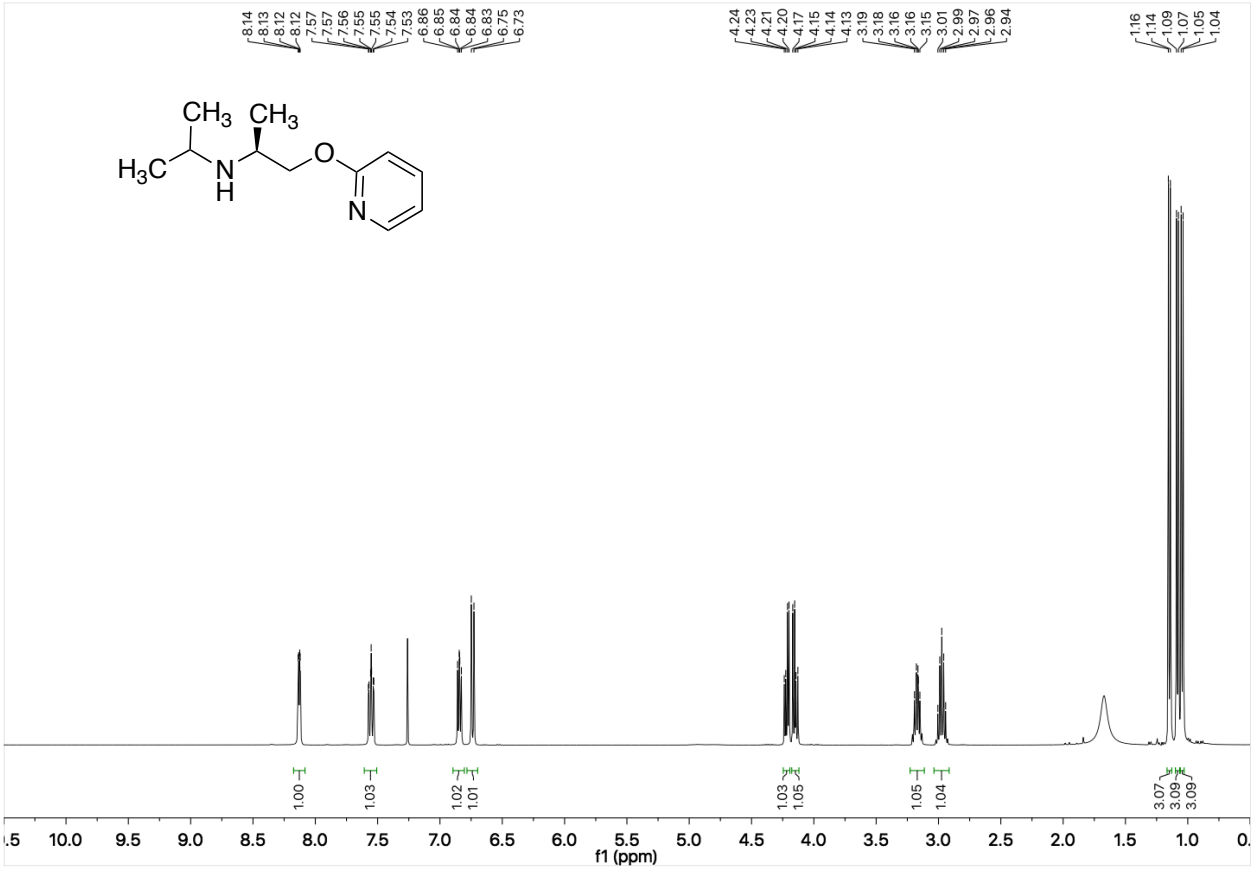


^{13}C NMR ($CDCl_3$, 100 MHz)

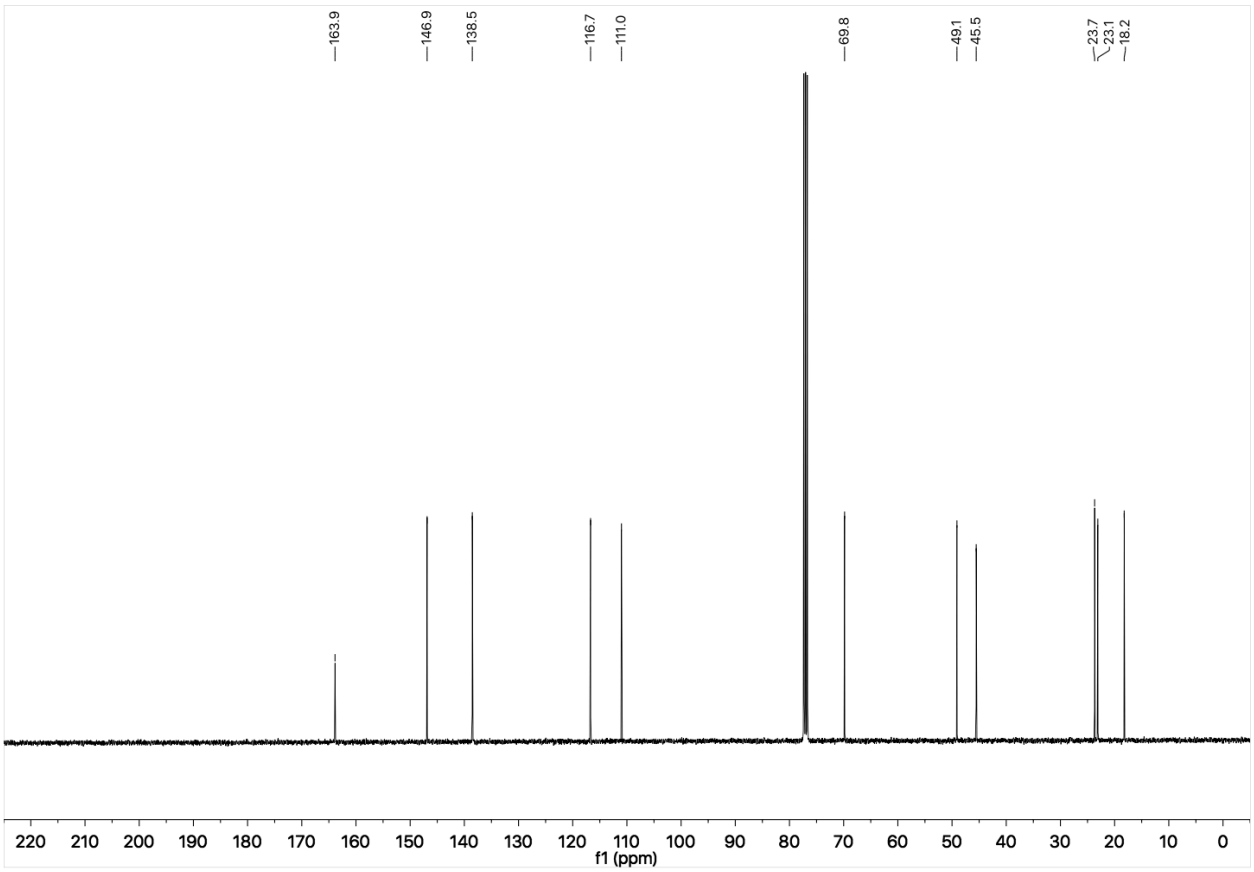


(S)-N-Isopropyl-1-(pyridin-2-yloxy)propan-2-amine (**350**)

^{1}H NMR ($CDCl_3$, 400 MHz)

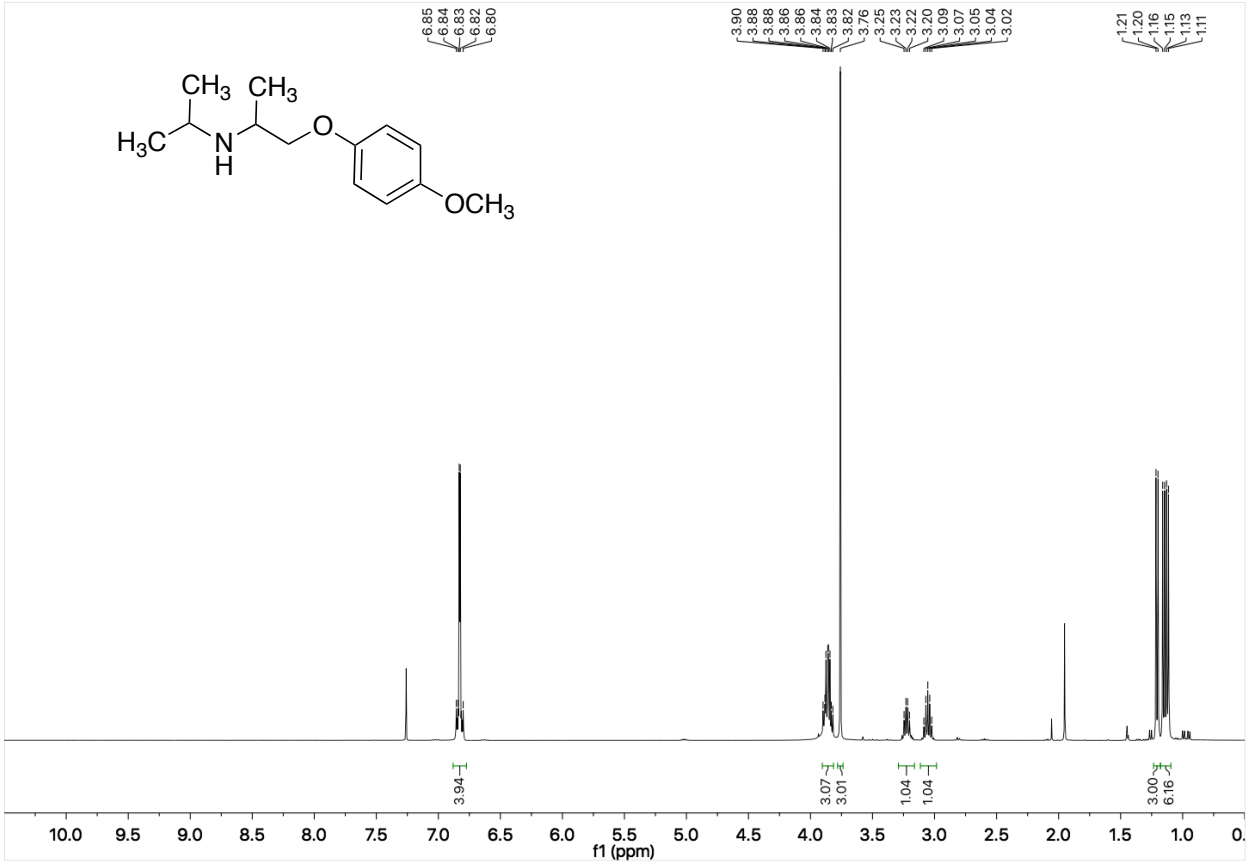


^{13}C NMR ($CDCl_3$, 100 MHz)

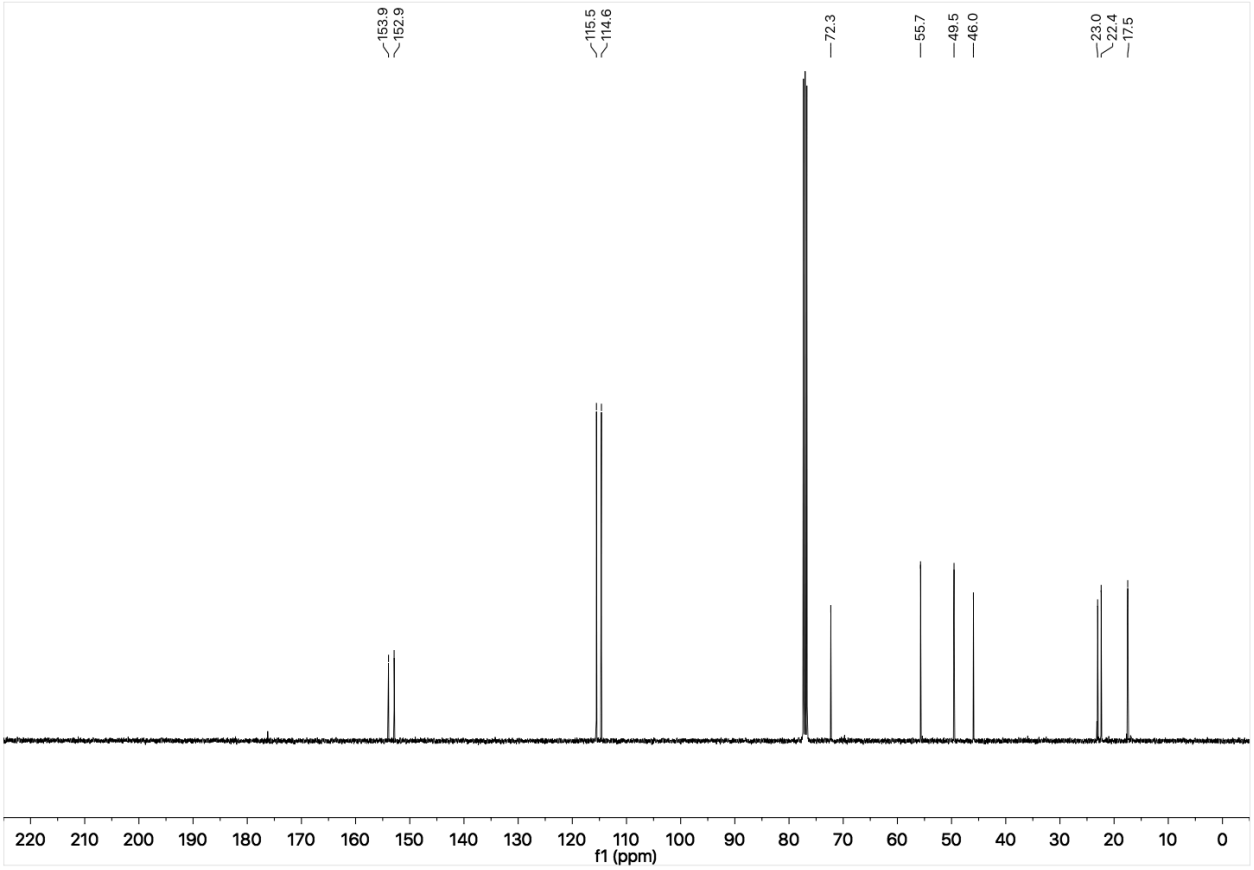


N-Isopropyl-1-(4-methoxyphenoxy)propan-2-amine (**351**)

^{1}H NMR ($CDCl_3$, 400 MHz)

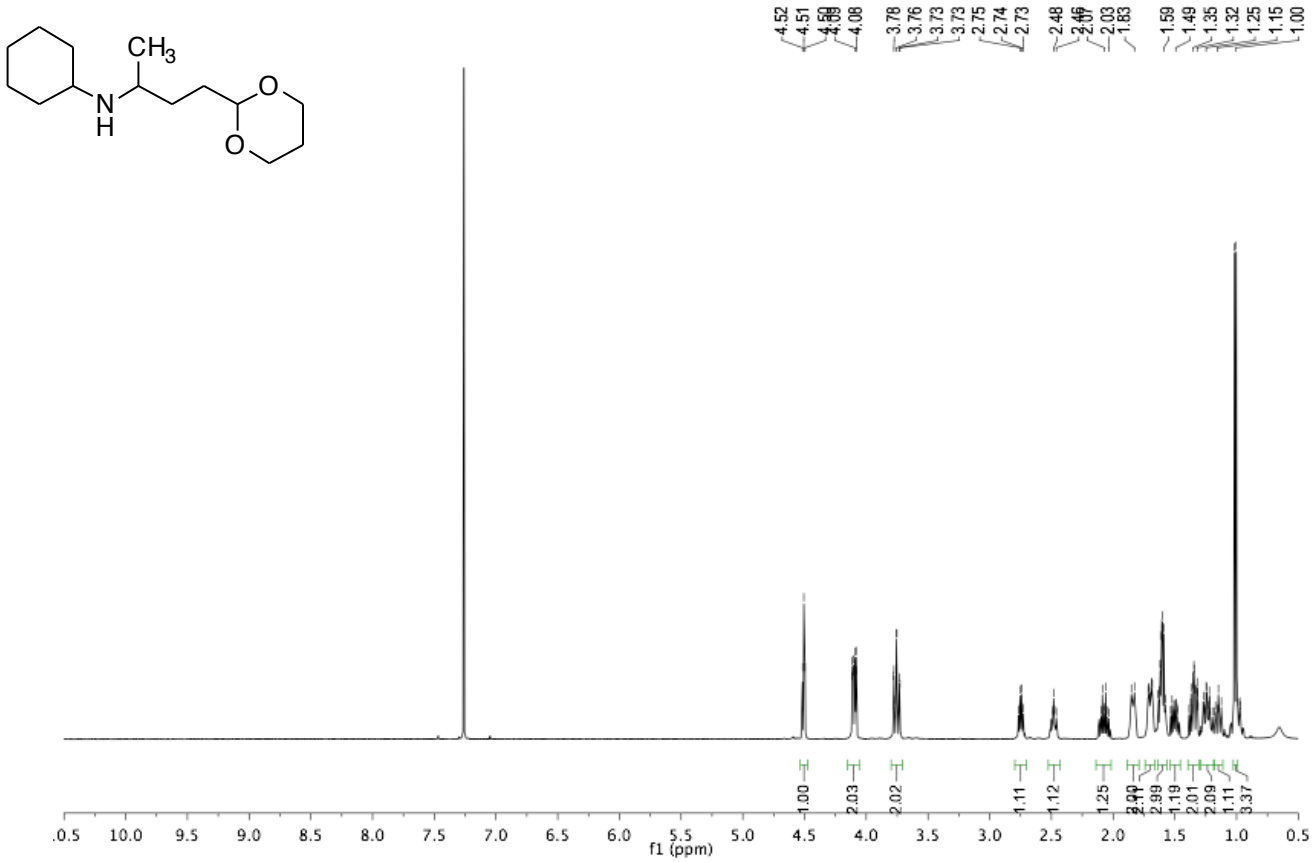


^{13}C NMR ($CDCl_3$, 100 MHz)

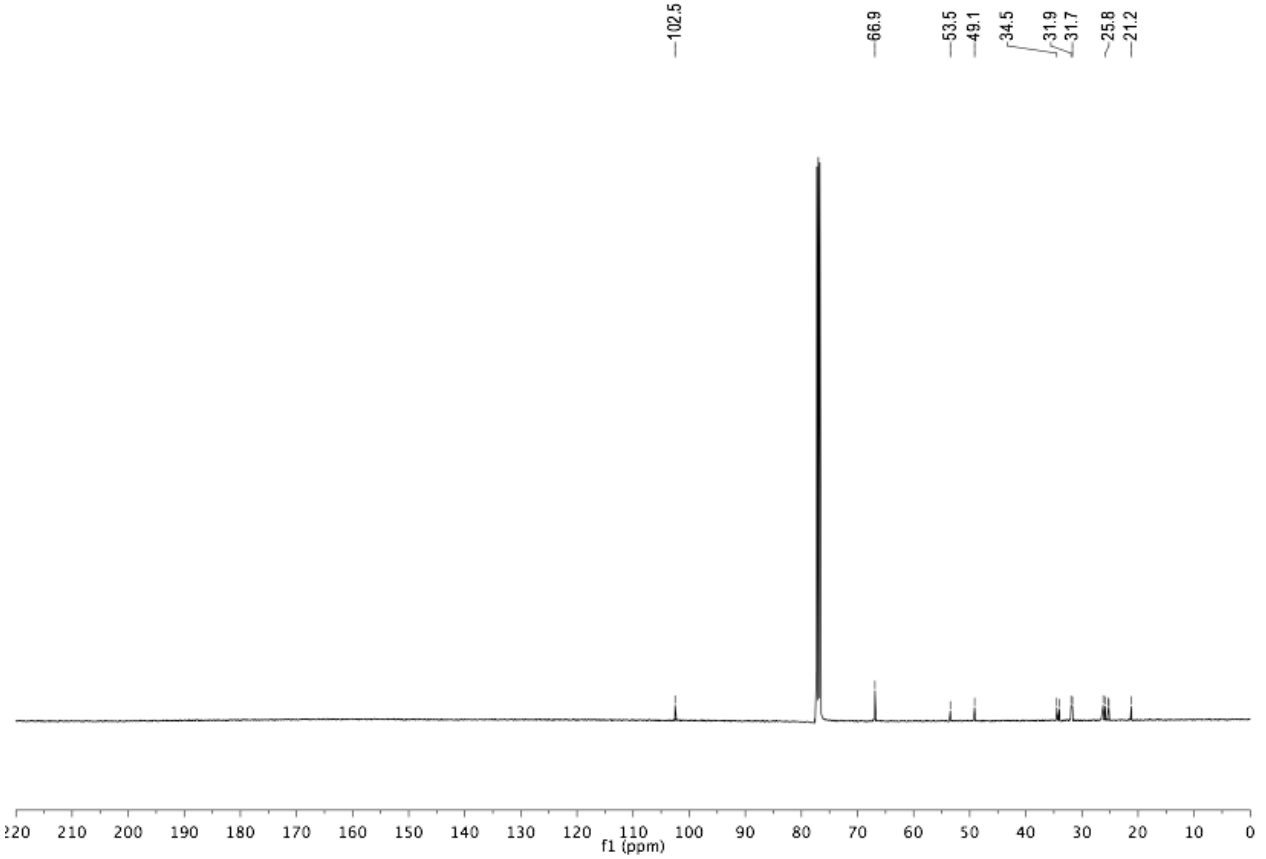


N-(4-(1,3-Dioxan-2-yl)butan-2-yl)cyclohexanamine (**352**)

^{1}H NMR ($CDCl_3$, 400 MHz)

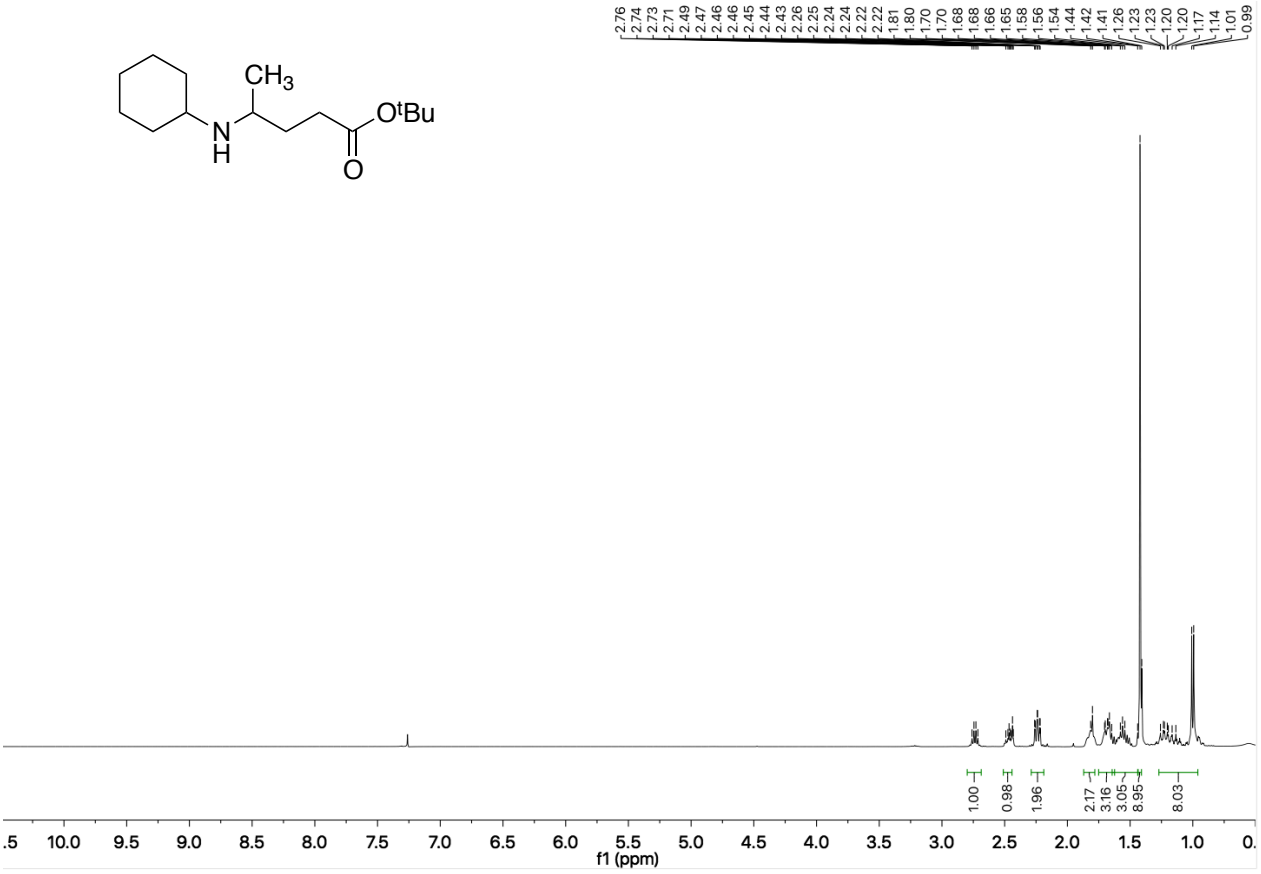


^{13}C NMR ($CDCl_3$, 100 MHz)

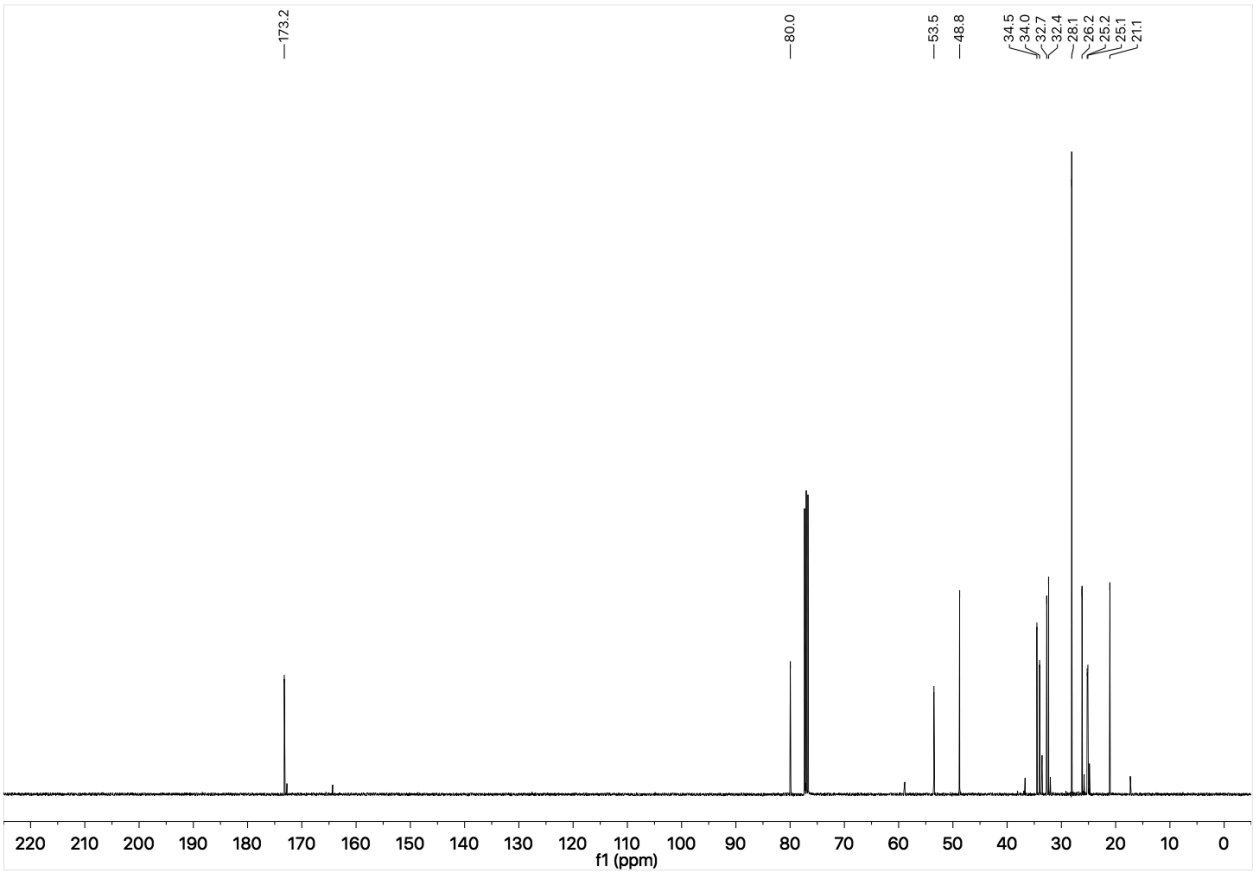


tert-Butyl 4-(cyclohexylamino)pentanoate (**353**)

^{1}H NMR ($CDCl_3$, 400 MHz)

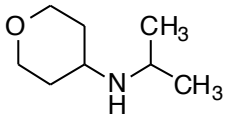


^{13}C NMR ($CDCl_3$, 100 MHz)

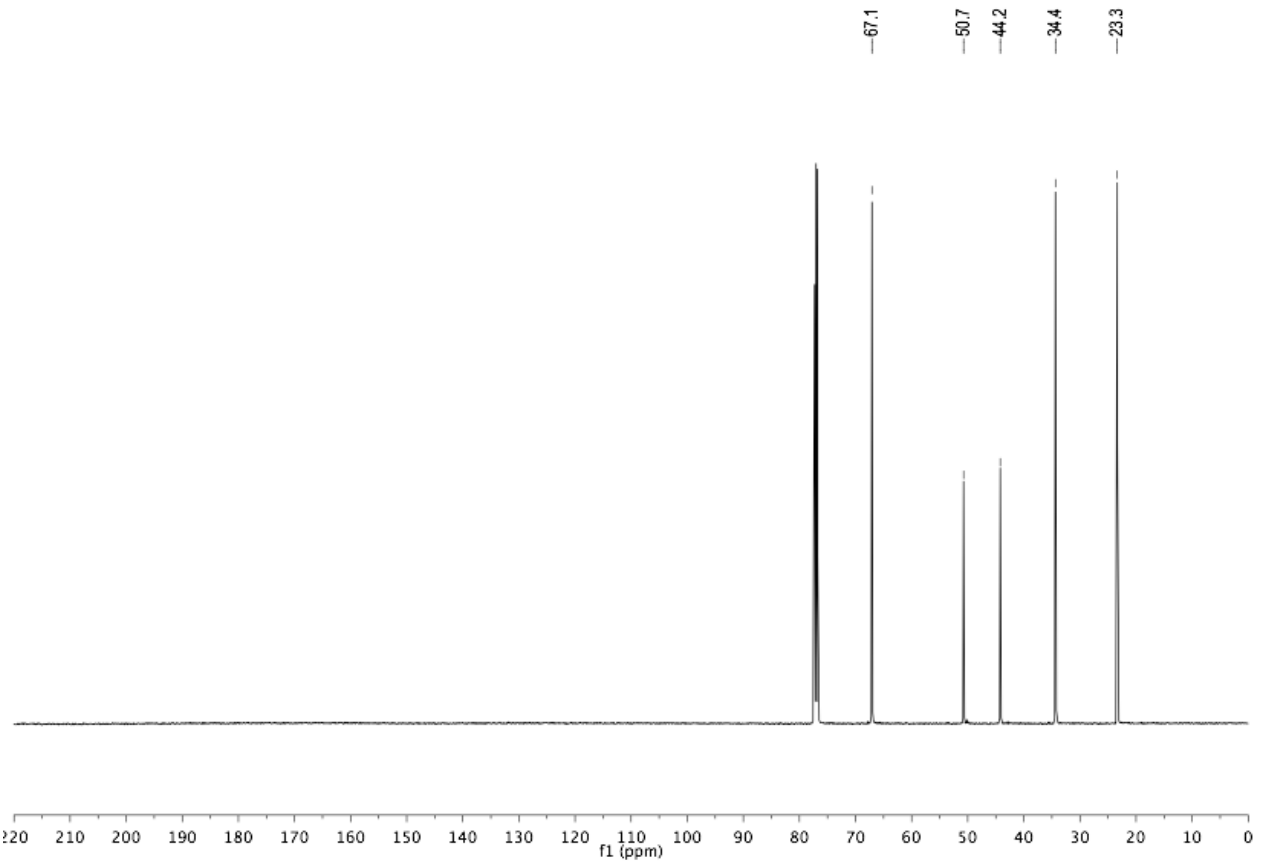


N-Isopropyltetrahydro-2H-pyran-4-amine (**354**)

^{1}H NMR ($CDCl_3$, 400 MHz)

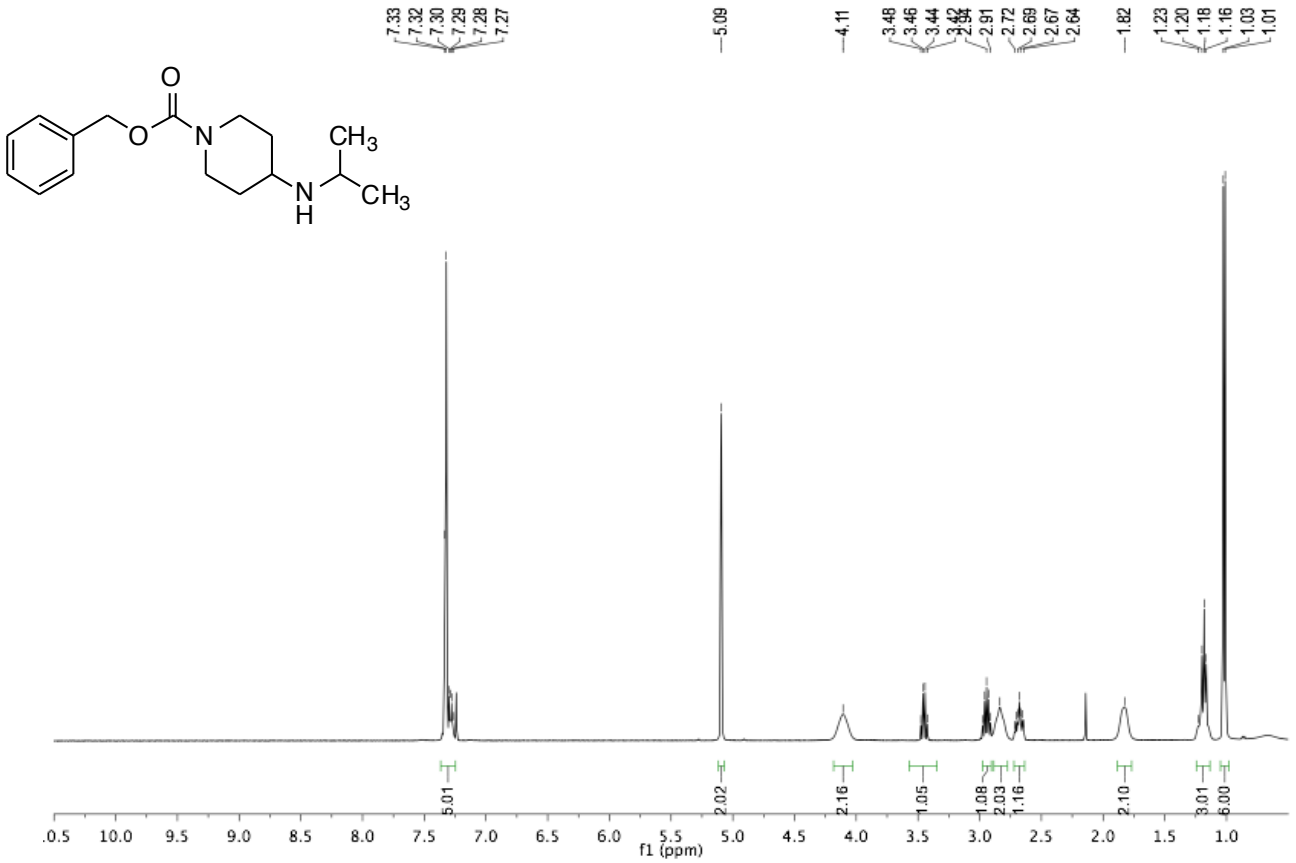


^{13}C NMR ($CDCl_3$, 100 MHz)

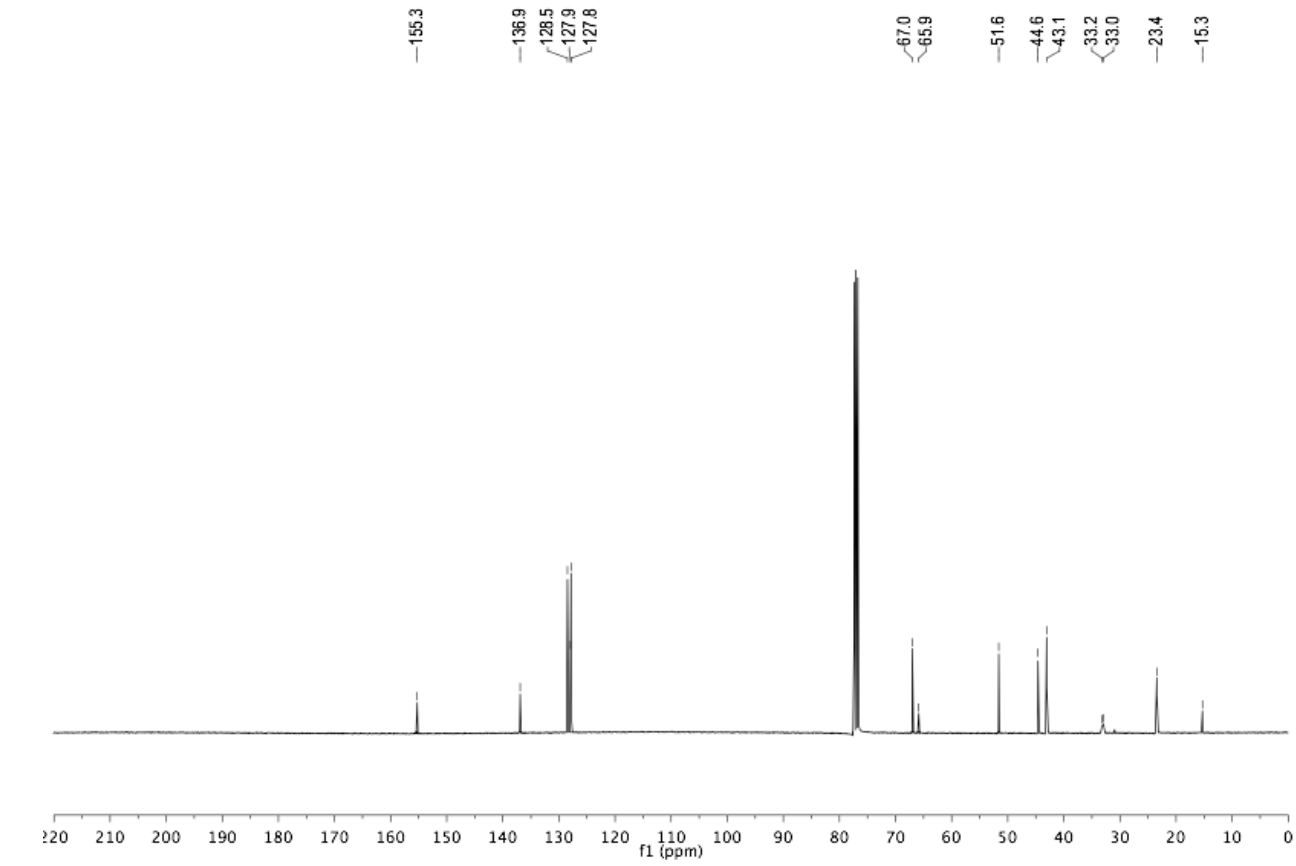


Benzyl 4-(isopropylamino)piperidine-1-carboxylate (**355**)

^{1}H NMR ($CDCl_3$, 400 MHz)

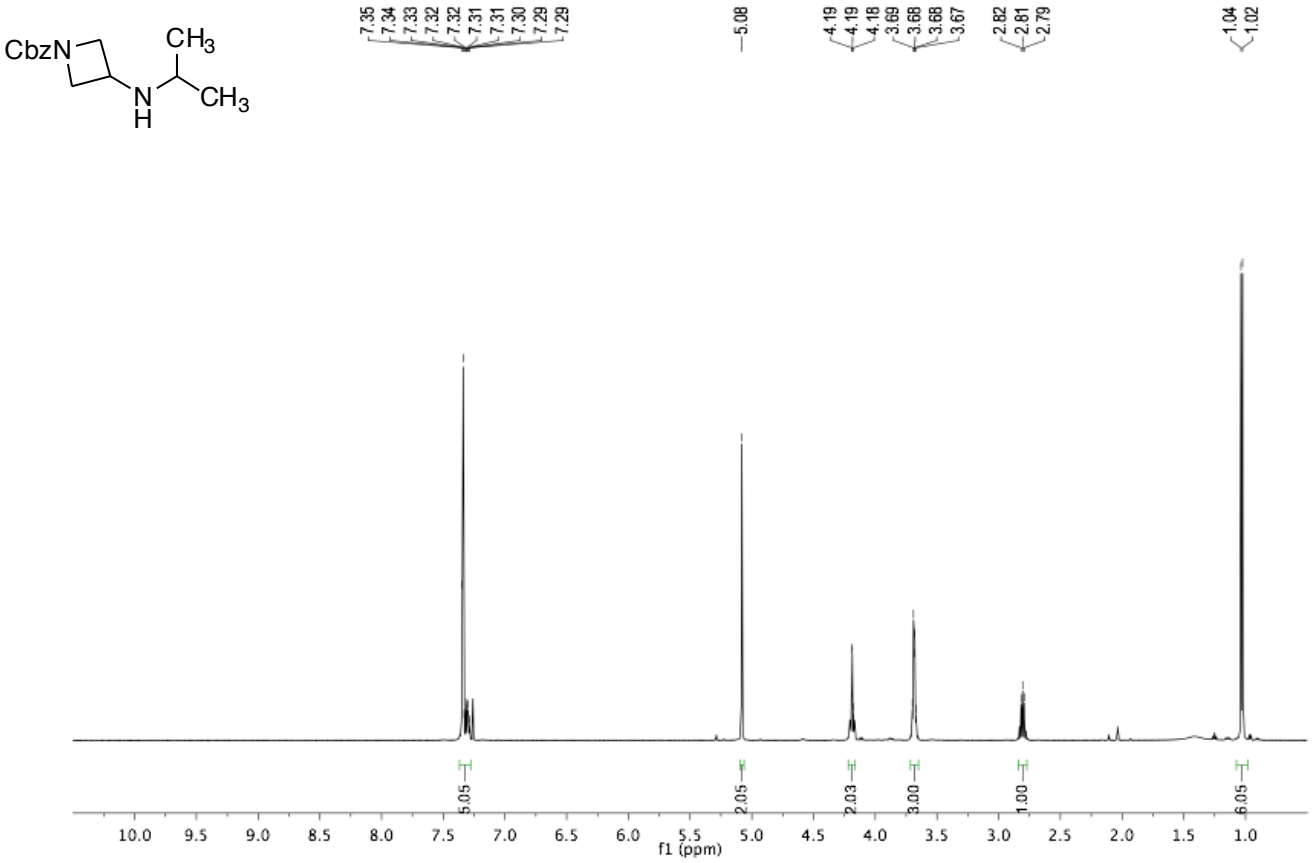


^{13}C NMR ($CDCl_3$, 100 MHz)

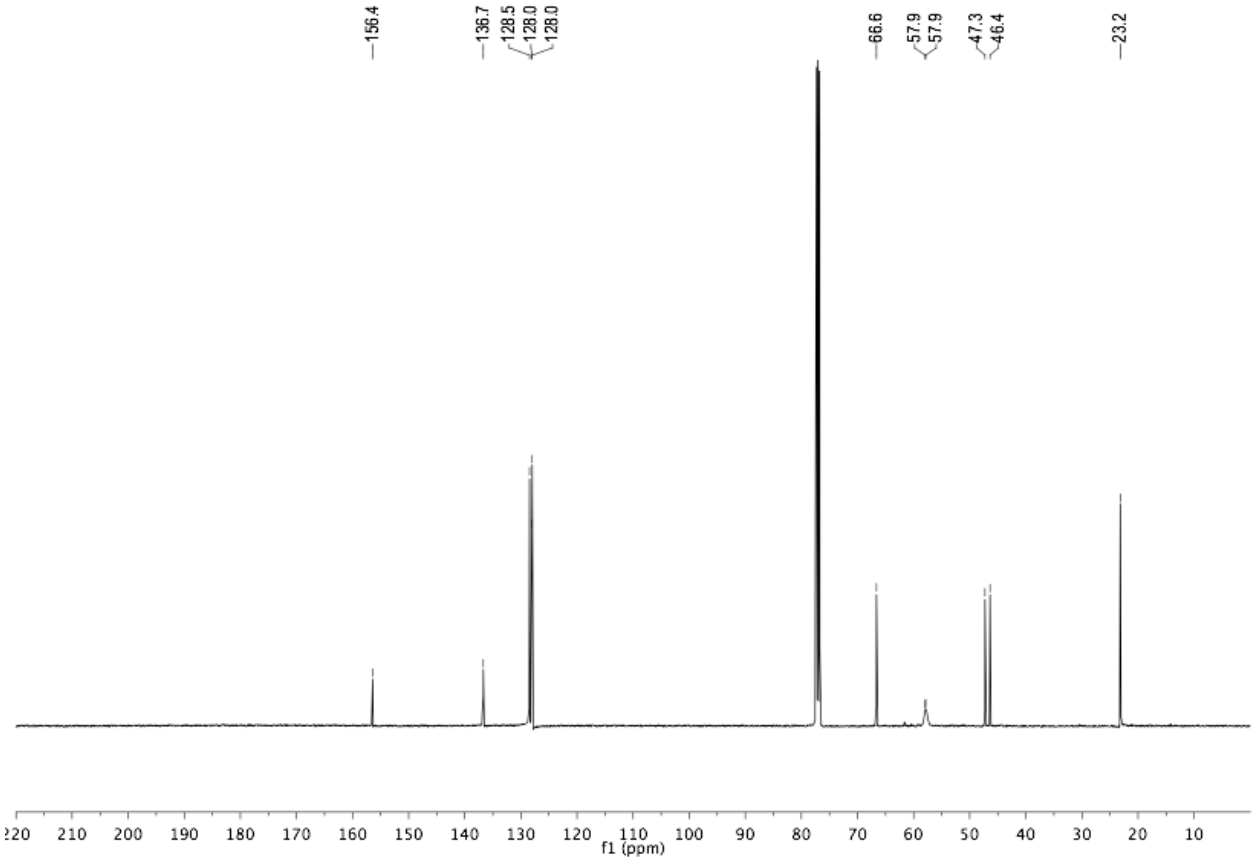


Benzyl 3-(isopropylamino)azetidine-1-carboxylate (**356**)

^{1}H NMR ($CDCl_3$, 400 MHz)

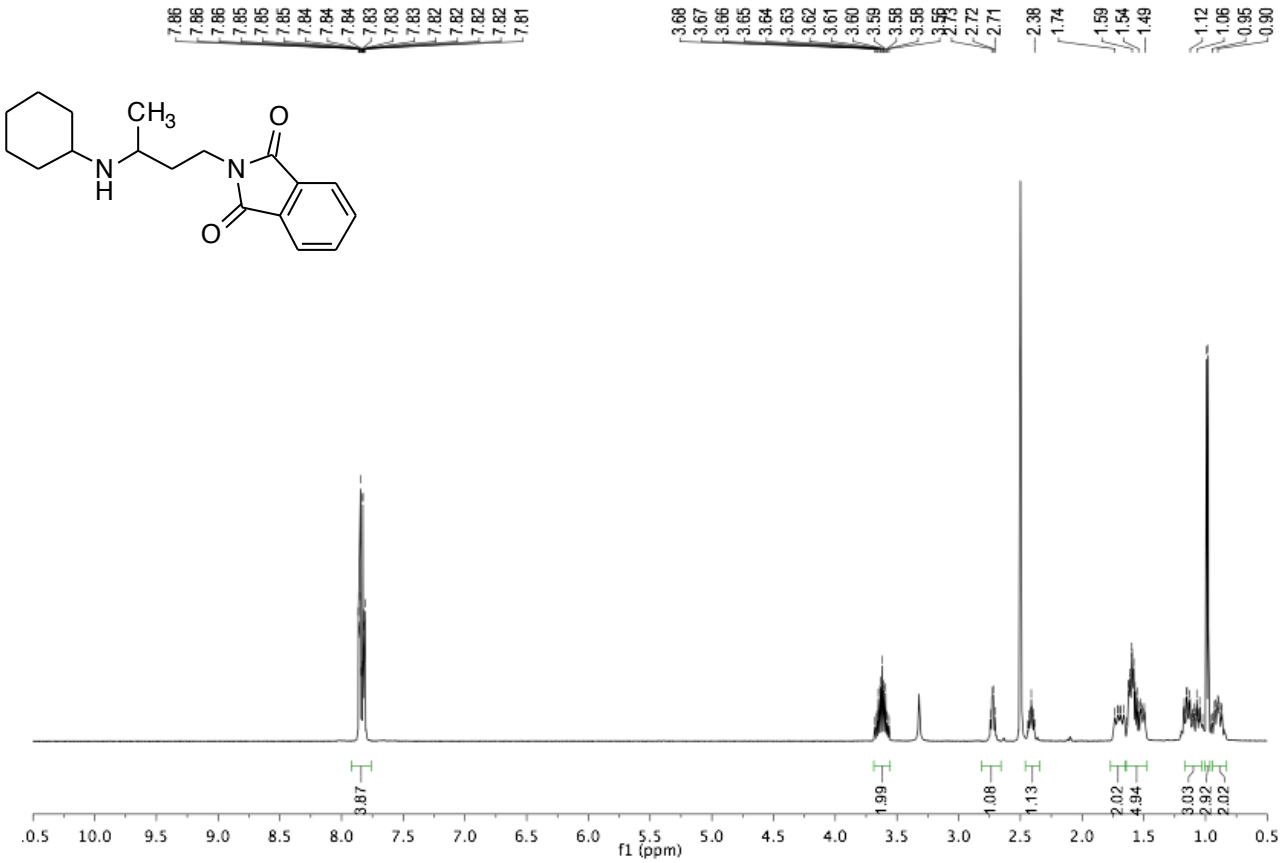


^{13}C NMR ($CDCl_3$, 100 MHz)

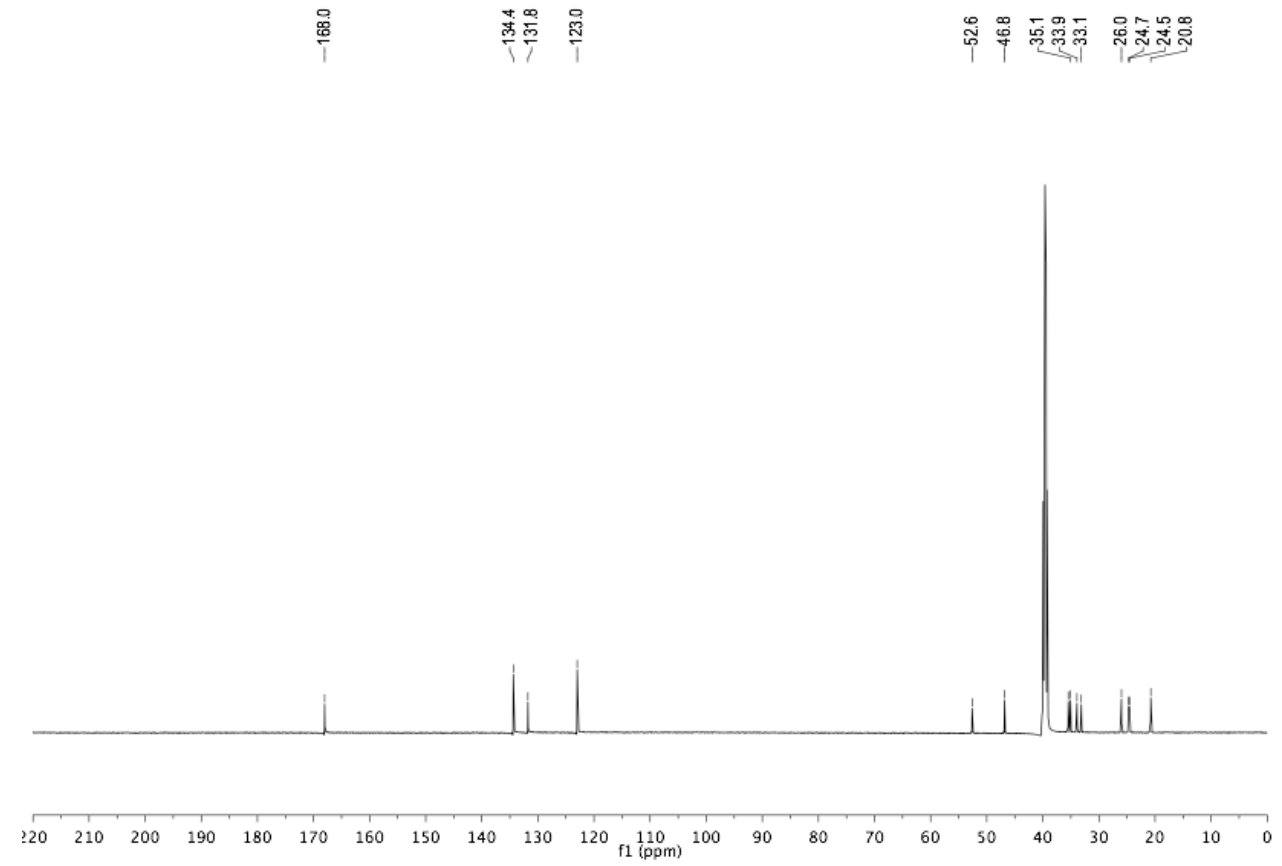


2-(3-(Cyclohexylamino)butyl)isoindoline-1,3-dione (**357**)

^{1}H NMR (d^{6}-DMSO, 400 MHz)

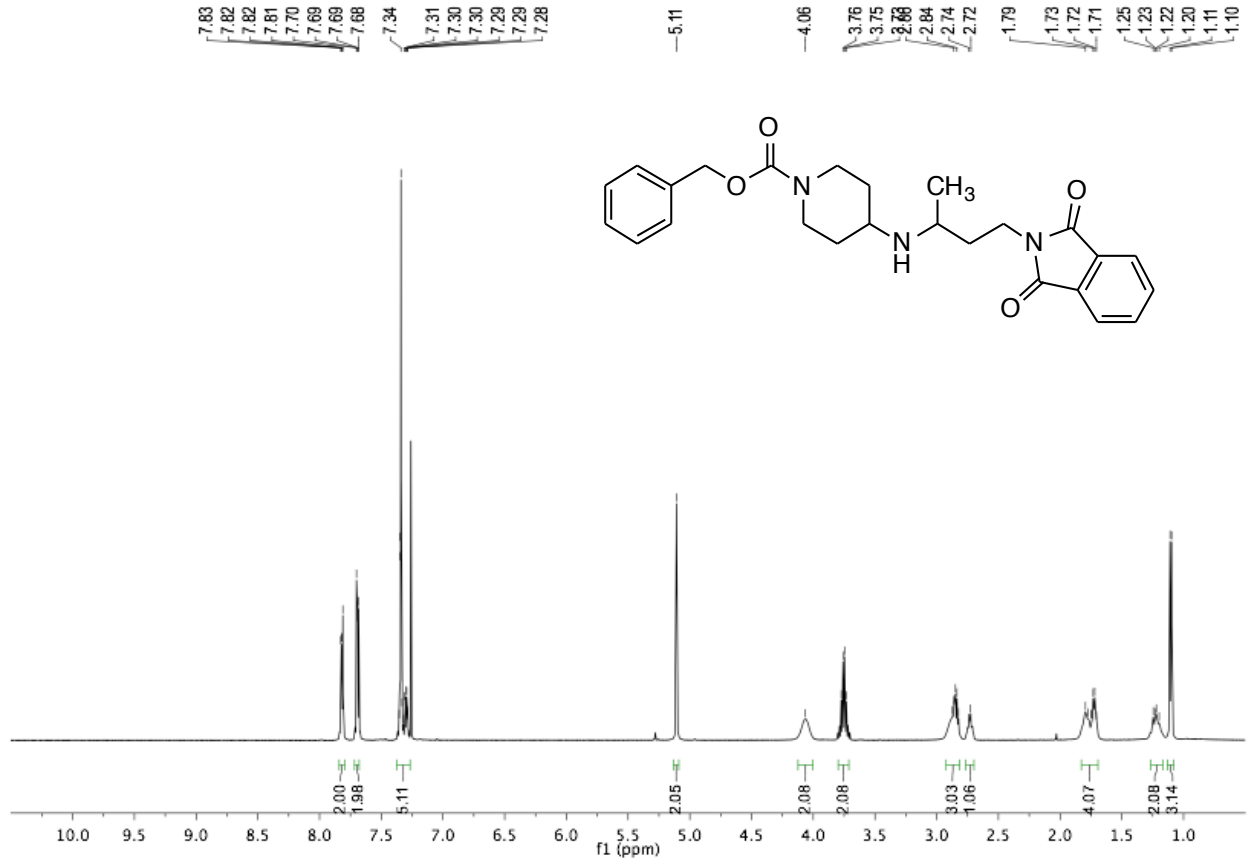


^{13}C NMR (d^{6}-DMSO, 100 MHz)

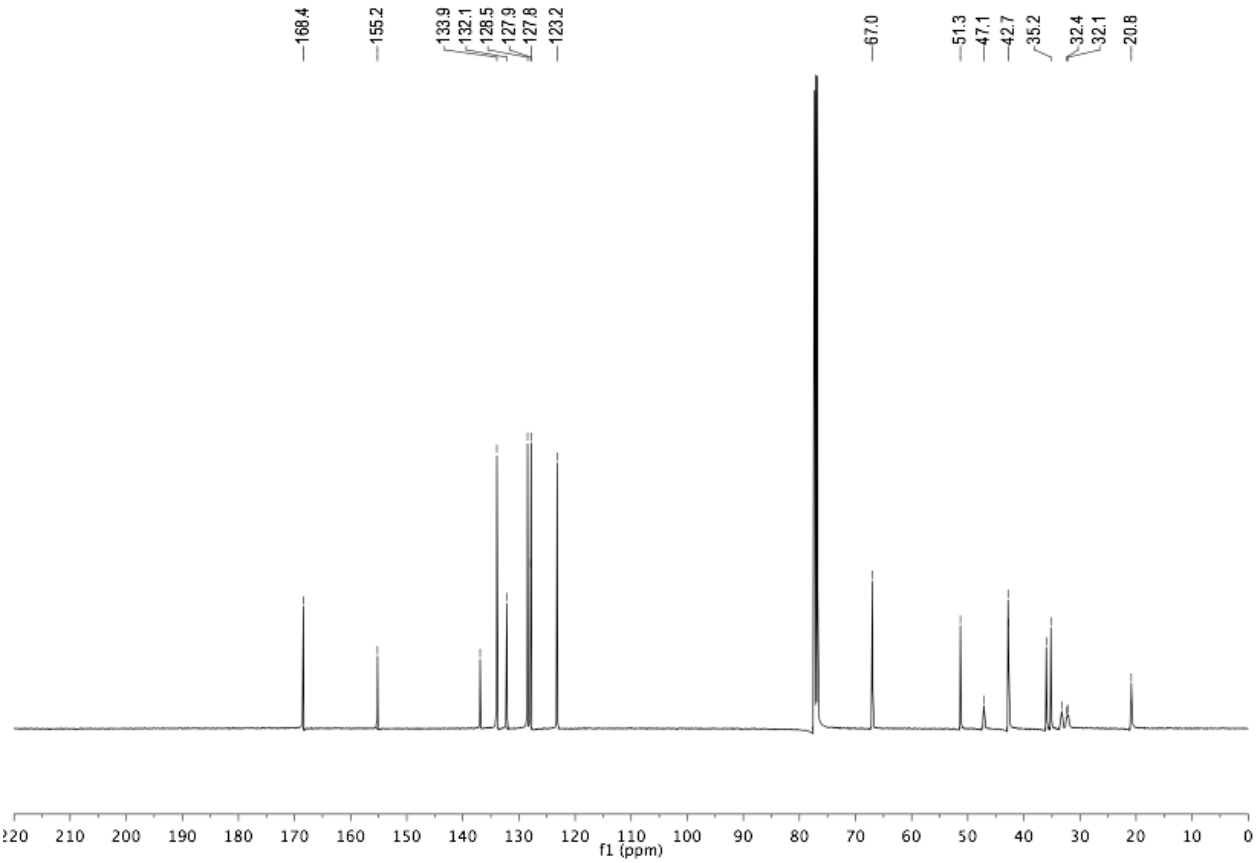


Benzyl 4-((4-(1,3-dioxoisoindolin-2-yl)butan-2-yl)amino)piperidine-1-carboxylate (**358**)

^{1}H NMR ($CDCl_3$, 400 MHz)

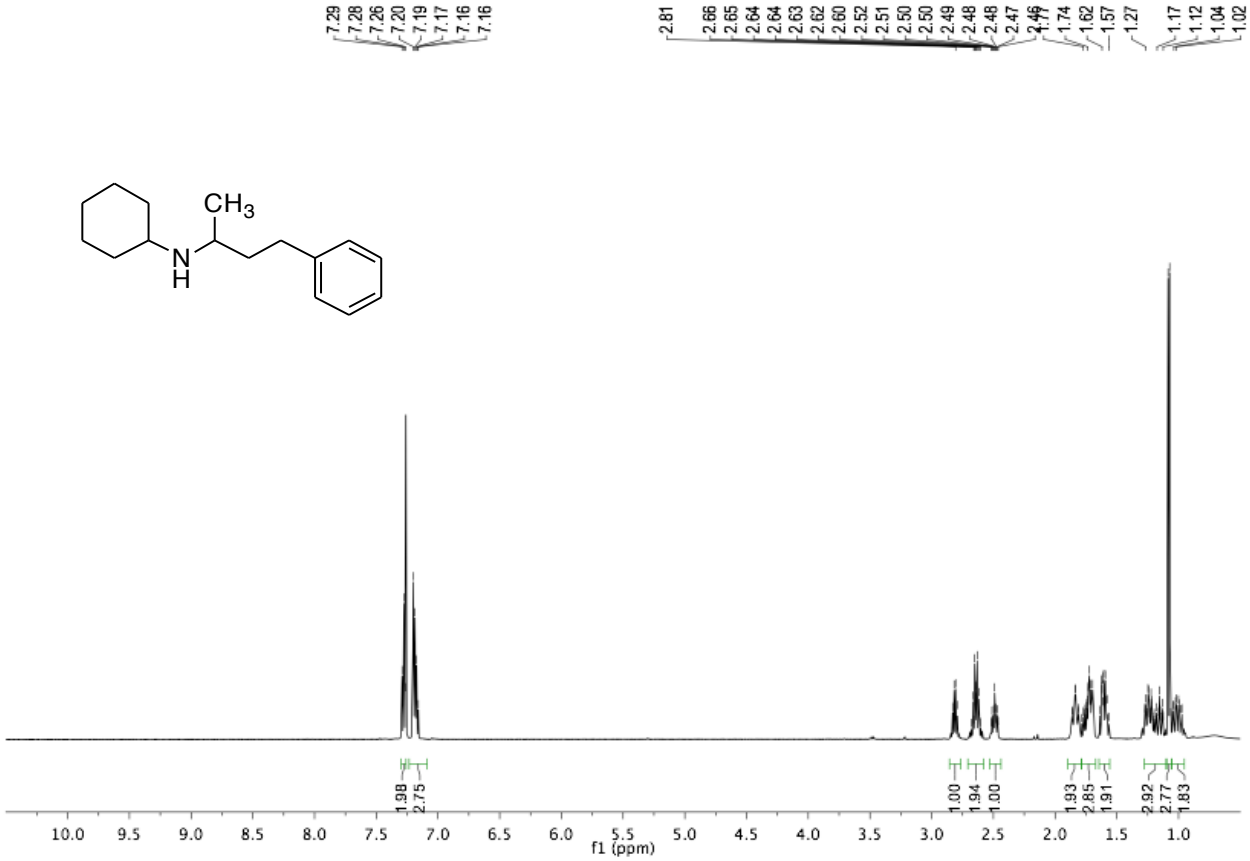


^{13}C NMR ($CDCl_3$, 100 MHz)

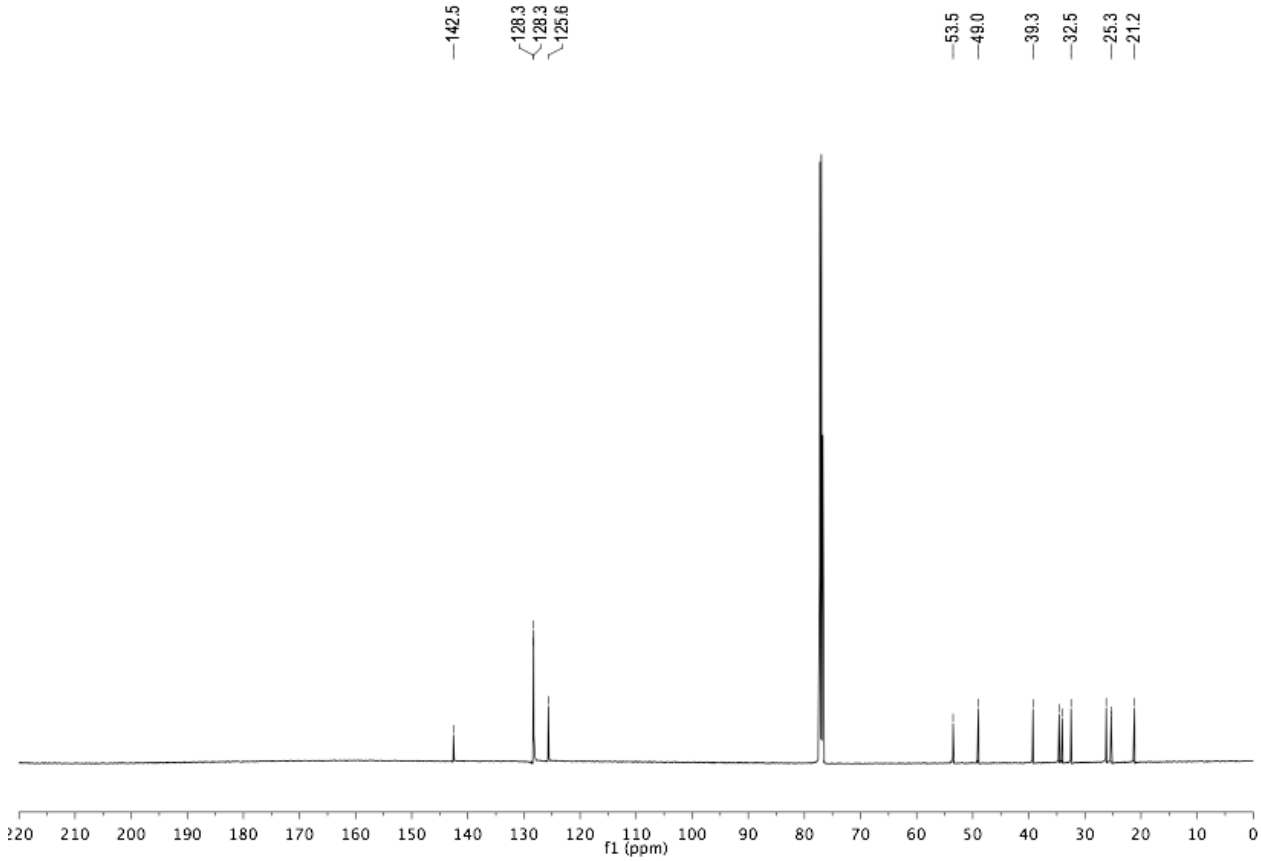


N-(4-Phenylbutan-2-yl)cyclohexanamine (**359**)

^{1}H NMR ($CDCl_3$, 400 MHz)

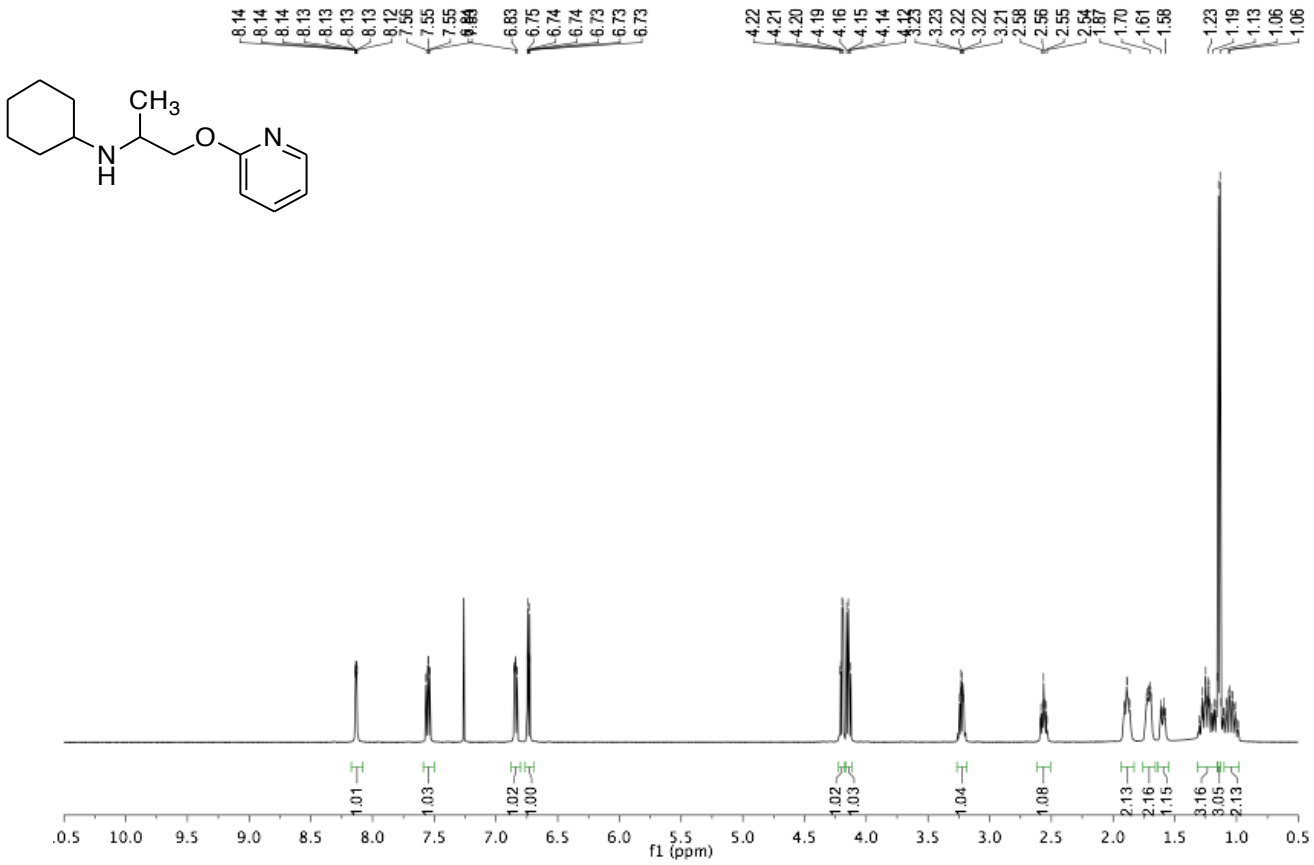


^{13}C NMR ($CDCl_3$, 100 MHz)

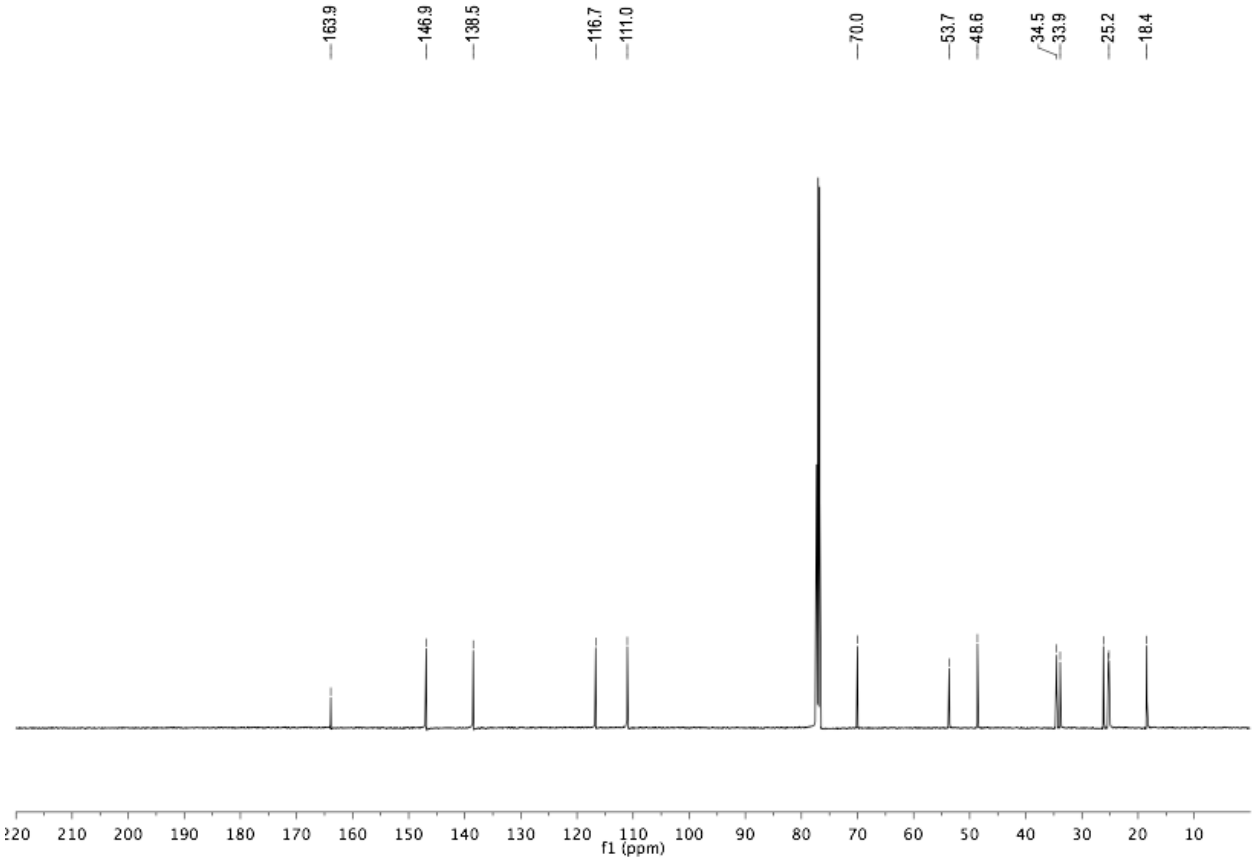


N-(1-(pyridin-2-yloxy)propan-2-yl)cyclohexanamine (**360**)

^{1}H NMR ($CDCl_3$, 400 MHz)

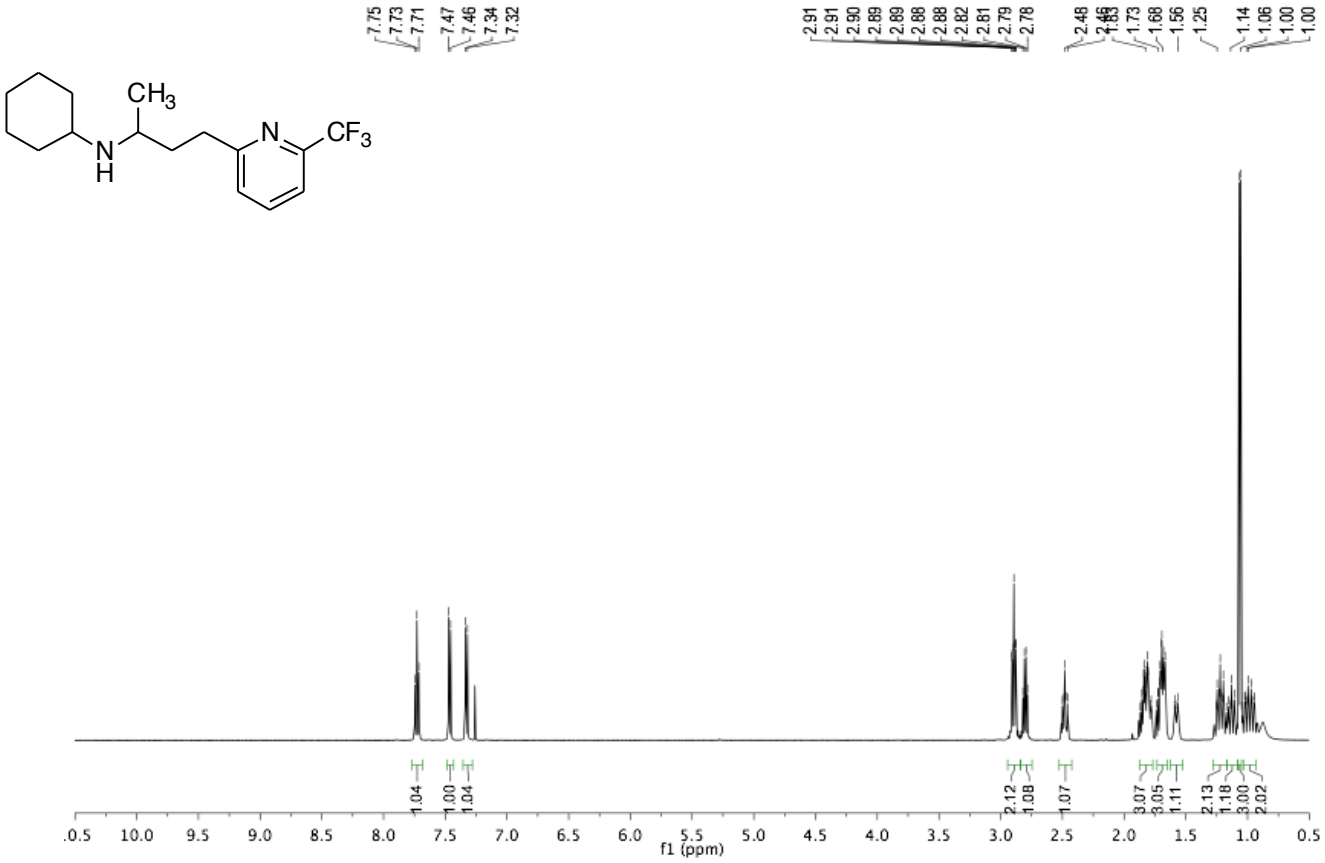


^{13}C NMR ($CDCl_3$, 100 MHz)

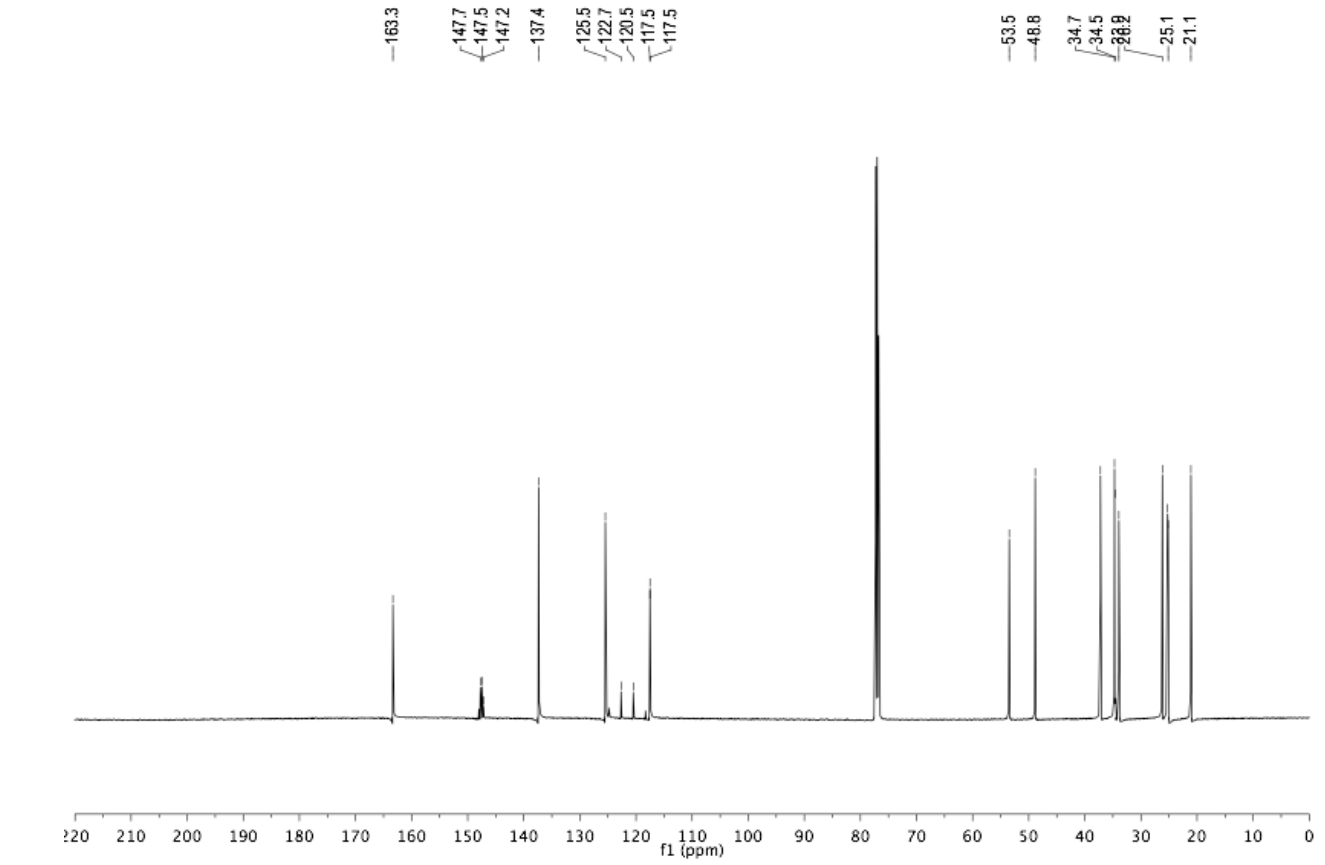


N-(4-(6-(Trifluoromethyl)pyridin-2-yl)butan-2-yl)cyclohexanamine (**361**)

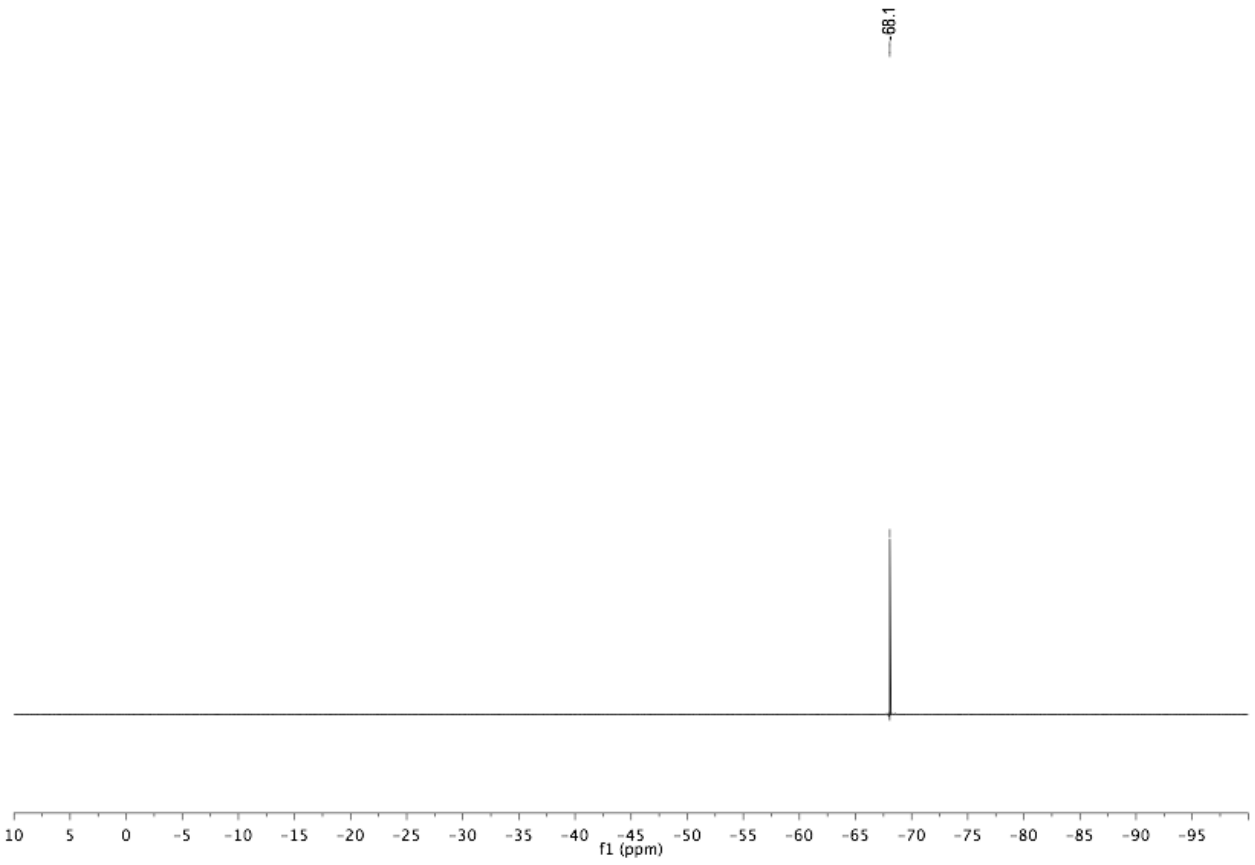
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)

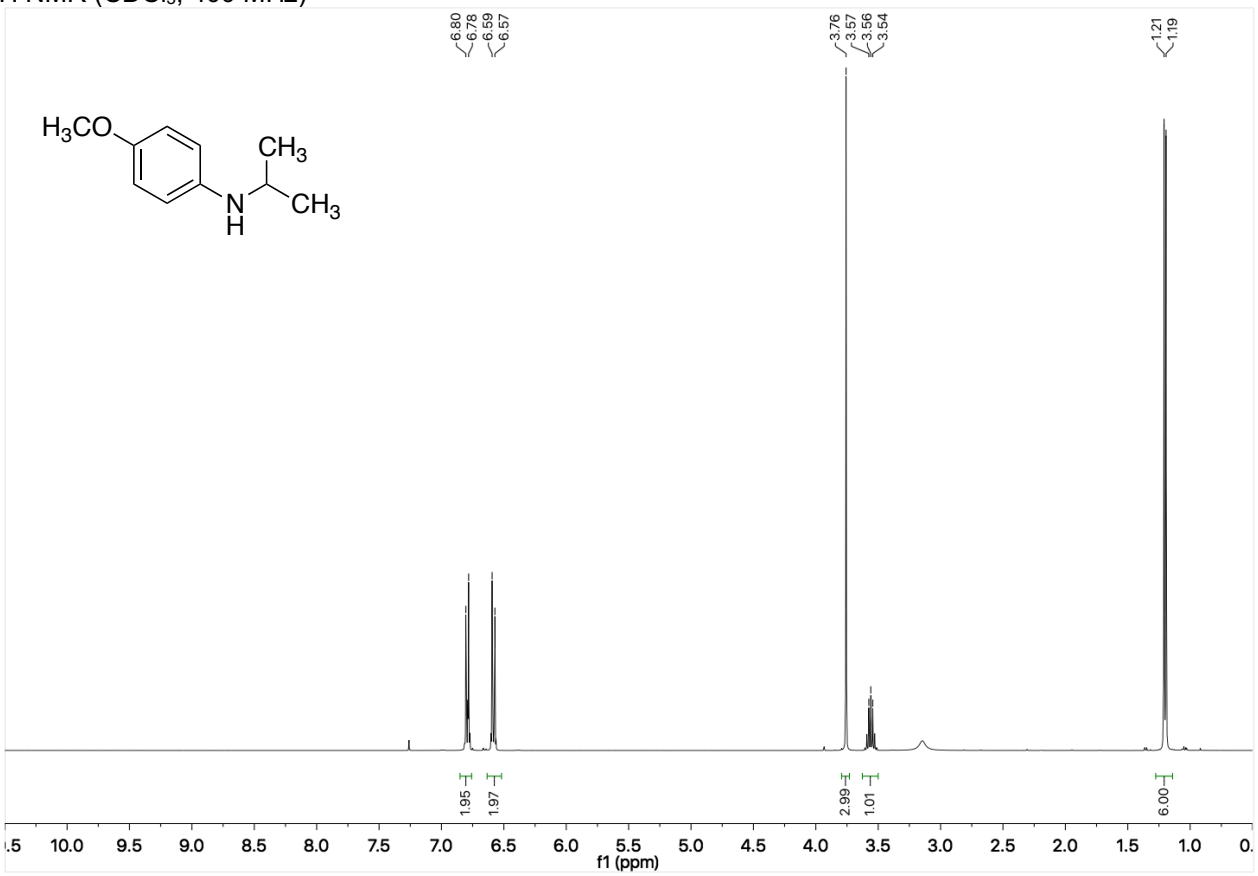


^{19}F NMR ($CDCl_3$, 376 MHz)

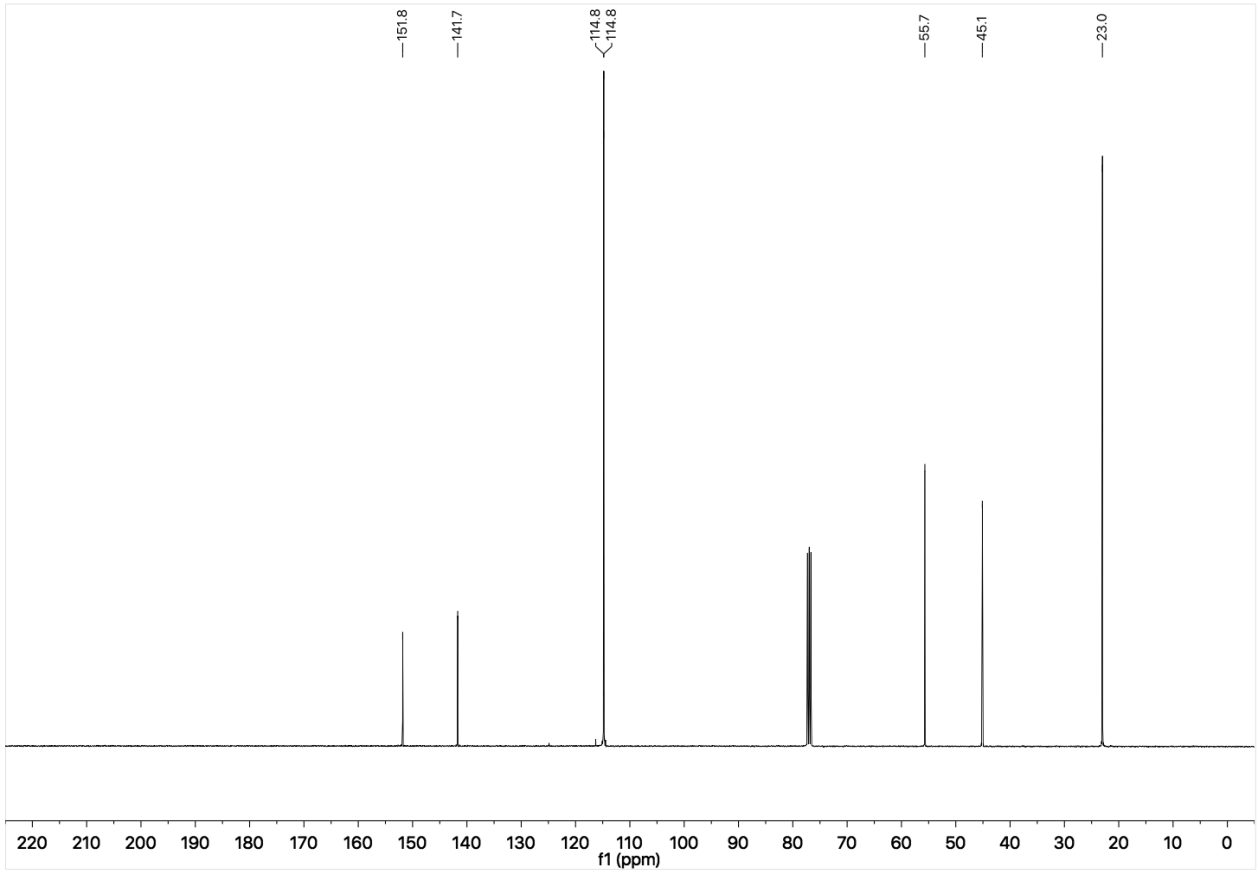


N-Isopropyl-4-methoxyaniline (**250**)

^{1}H NMR ($CDCl_3$, 400 MHz)

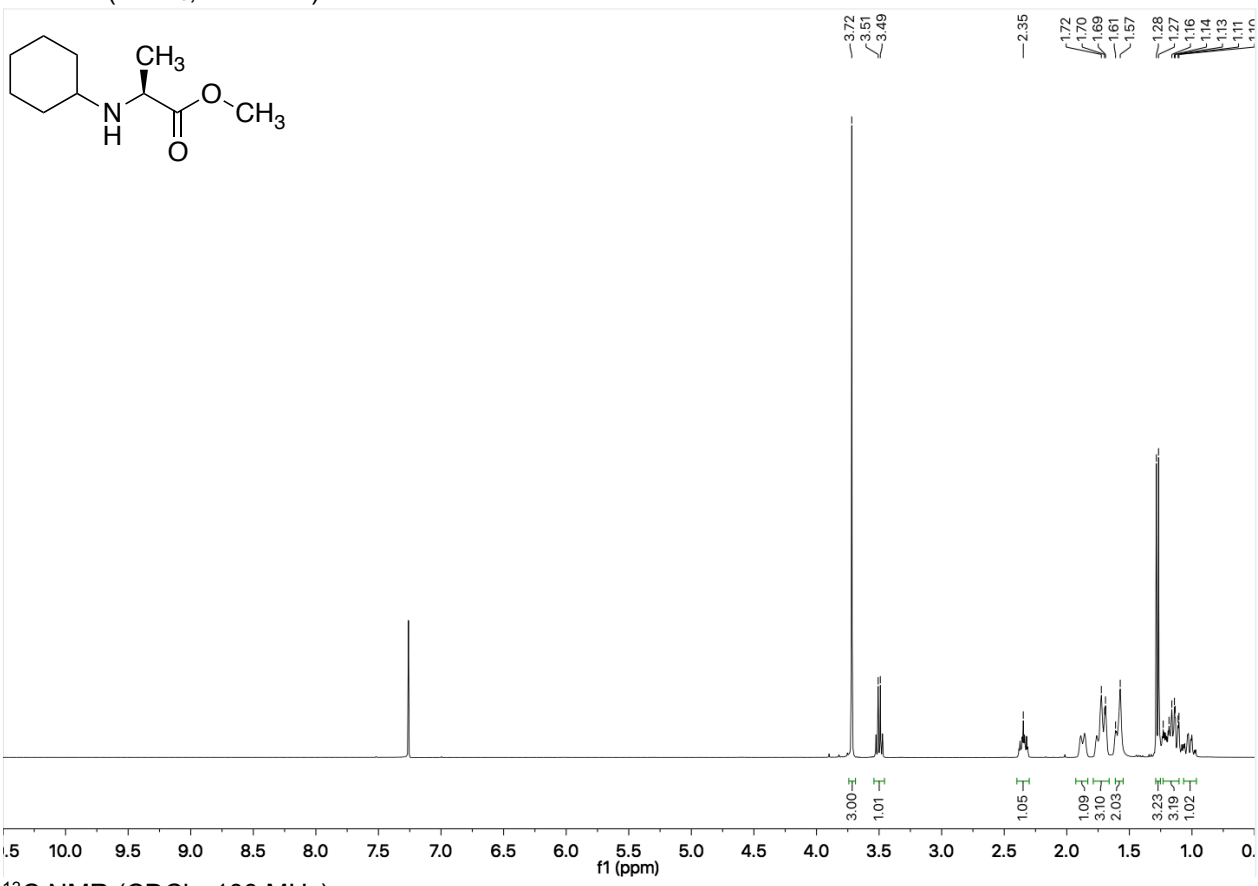


^{13}C NMR ($CDCl_3$, 100 MHz)

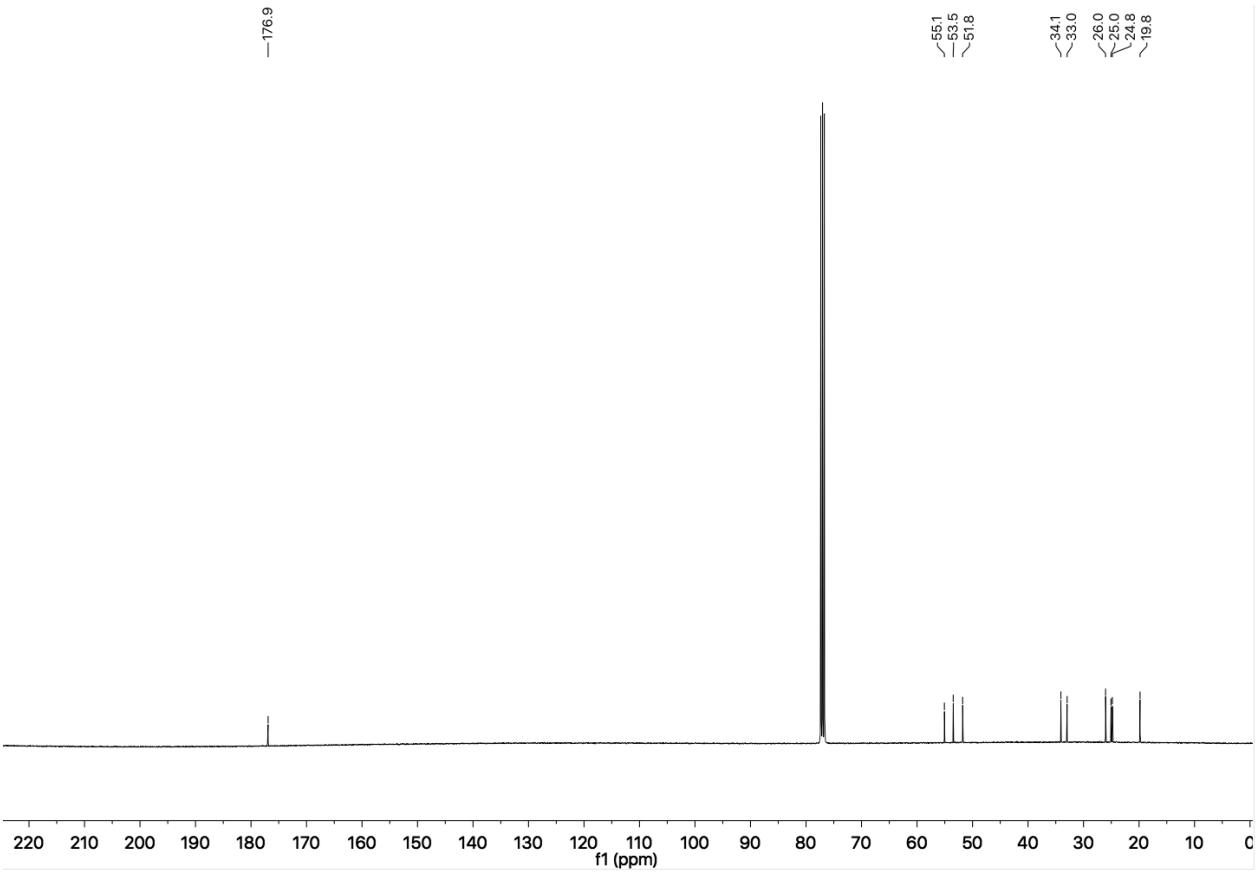


Methyl (2S)-2-(cyclohexylamino)propanoate (**251**)

^{1}H NMR ($CDCl_3$, 400 MHz)

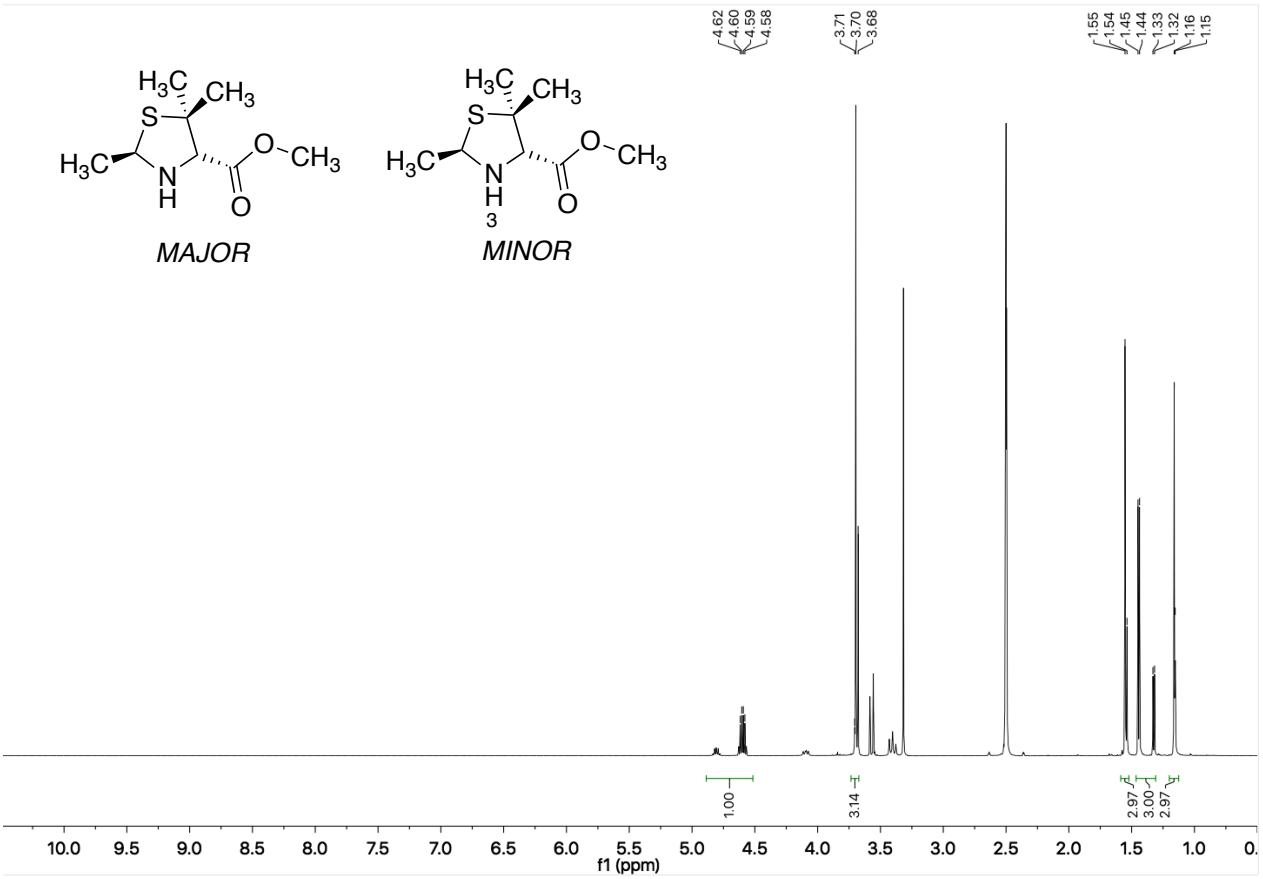


^{13}C NMR ($CDCl_3$, 100 MHz)



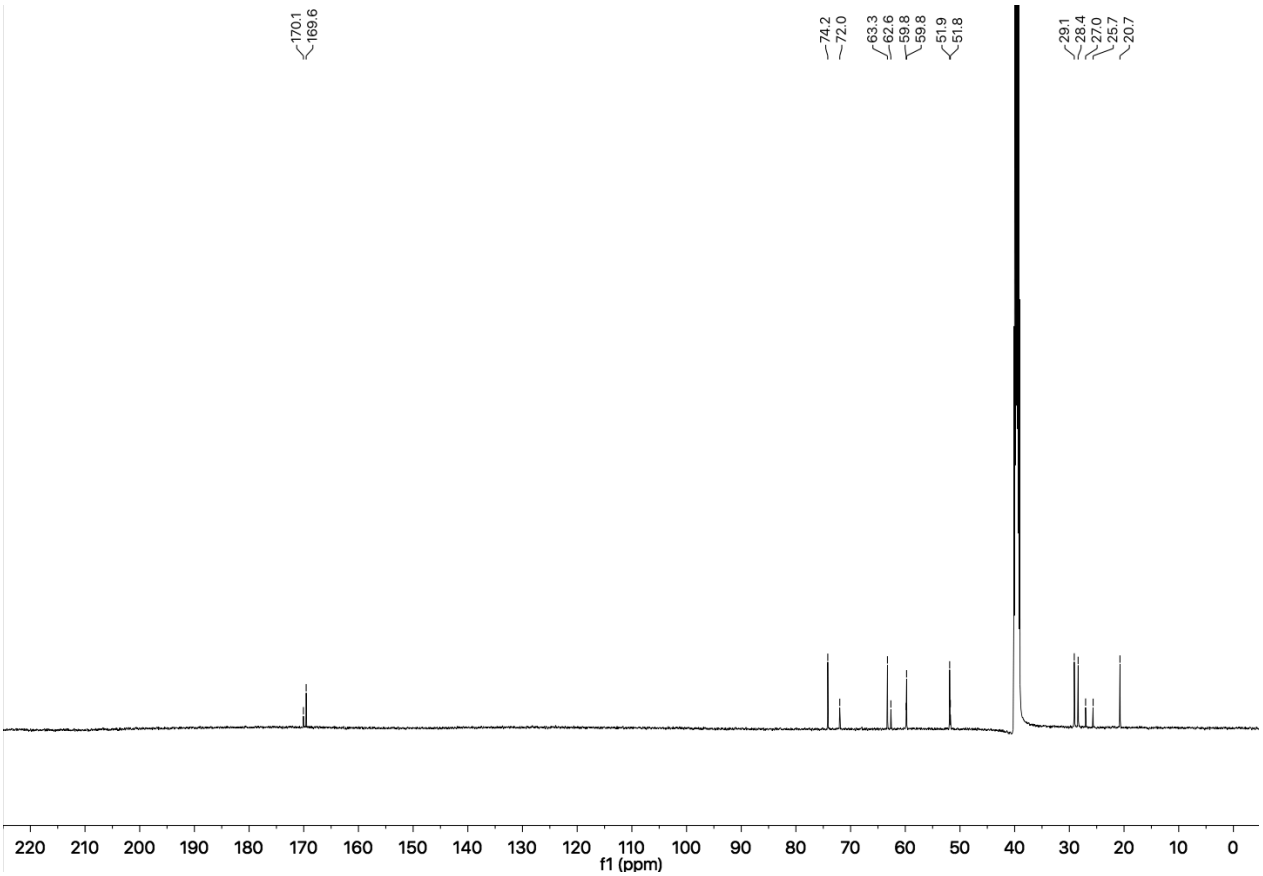
(2R,4S)-methyl 2,5,5-trimethylthiazolidine-4-carboxylate & (2S,4S)-methyl 2,5,5-trimethylthiazolidine-4-carboxylate (**254**)

^{1}H NMR ($CDCl_3$, 400 MHz)



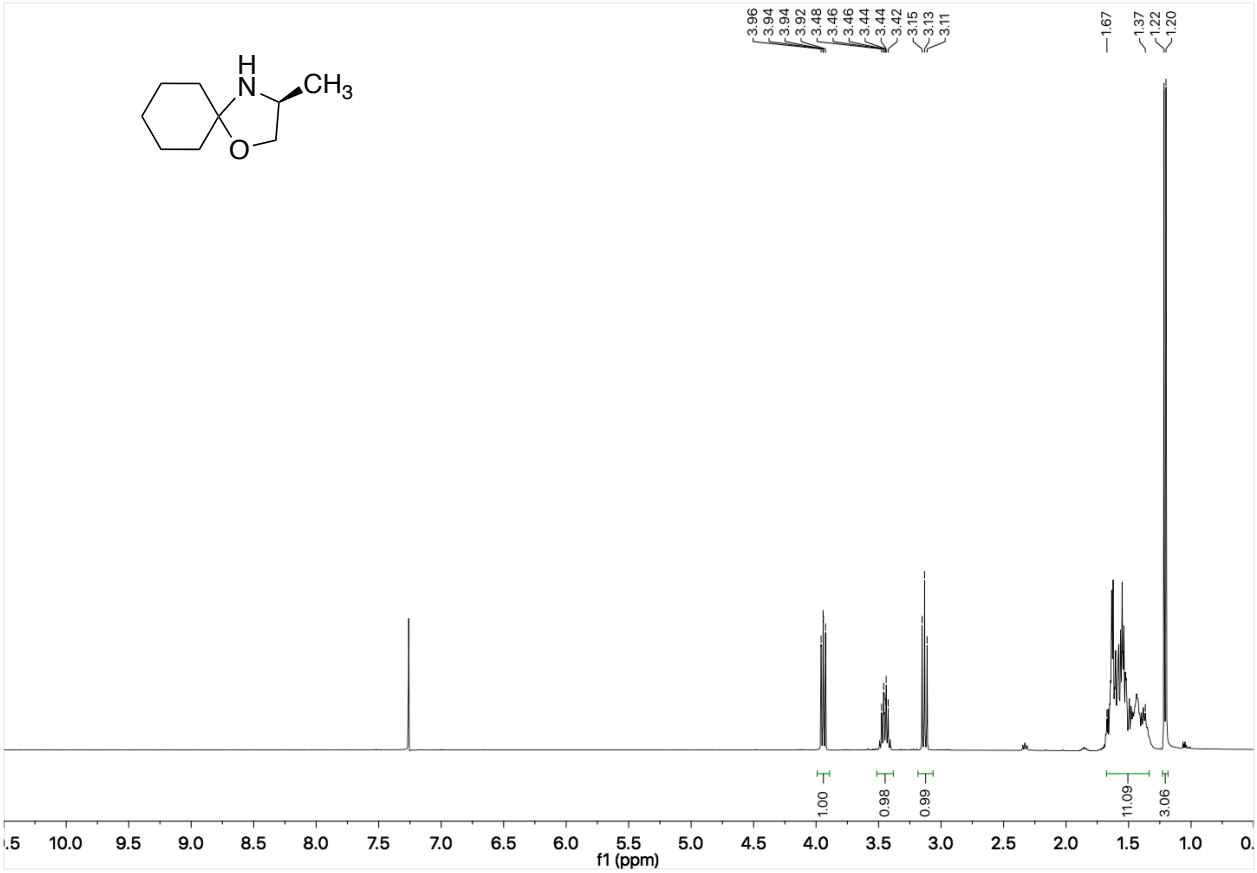
MAJOR *MINOR*

^{13}C NMR ($CDCl_3$, 100 MHz)

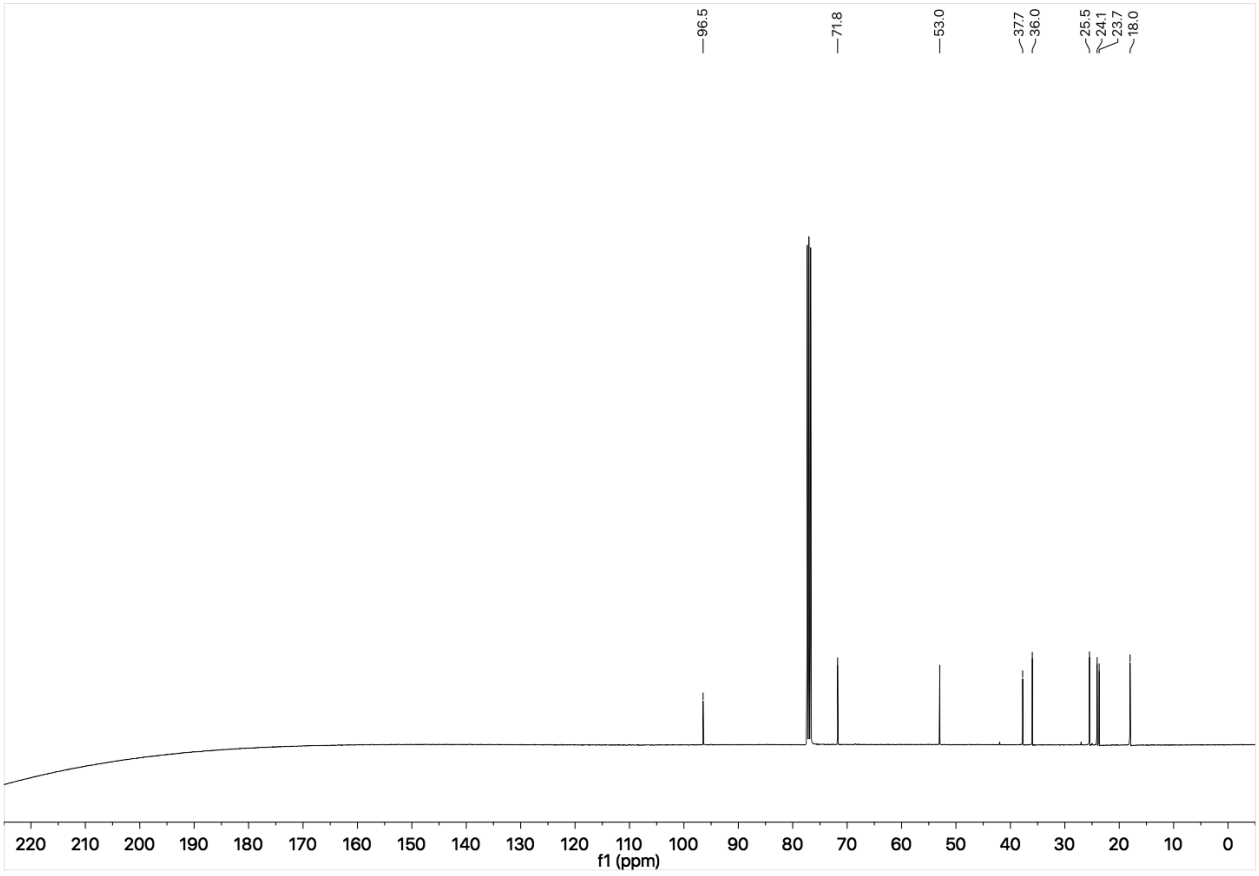


(S)-3-methyl-1-oxa-4-azaspiro[4.5]decane (**256**)

^{1}H NMR ($CDCl_3$, 400 MHz)

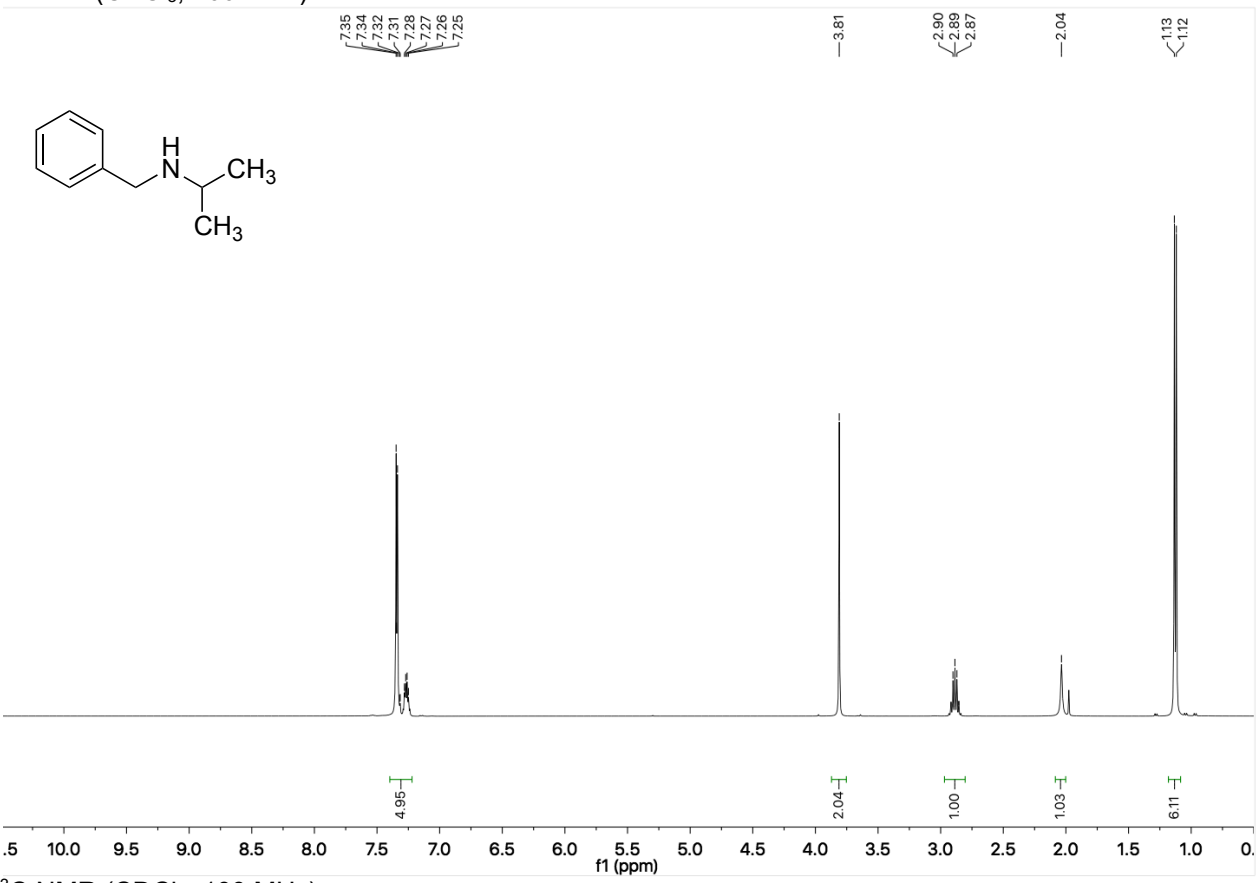


^{13}C NMR ($CDCl_3$, 100 MHz)

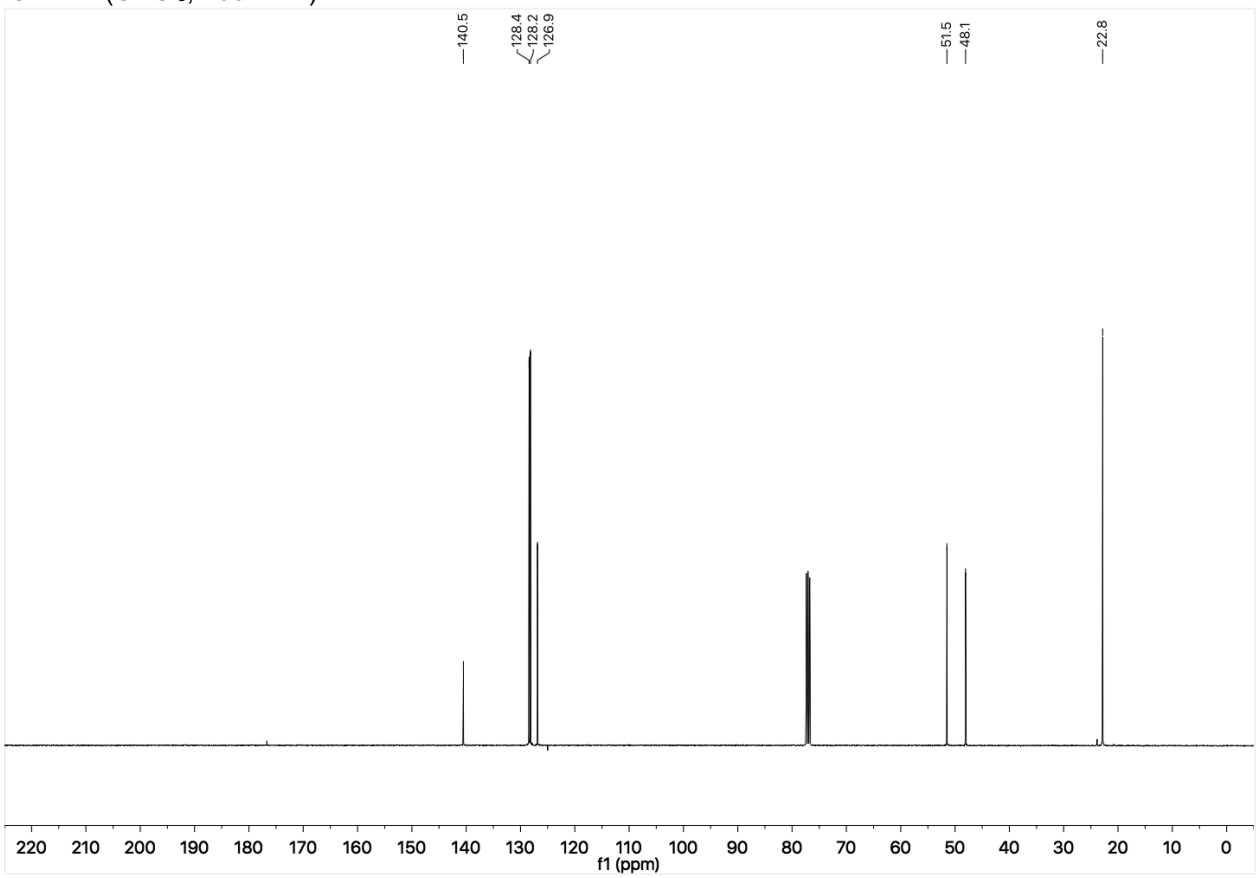


N-Benzylpropan-2-amine (**257**)

^{1}H NMR ($CDCl_3$, 400 MHz)

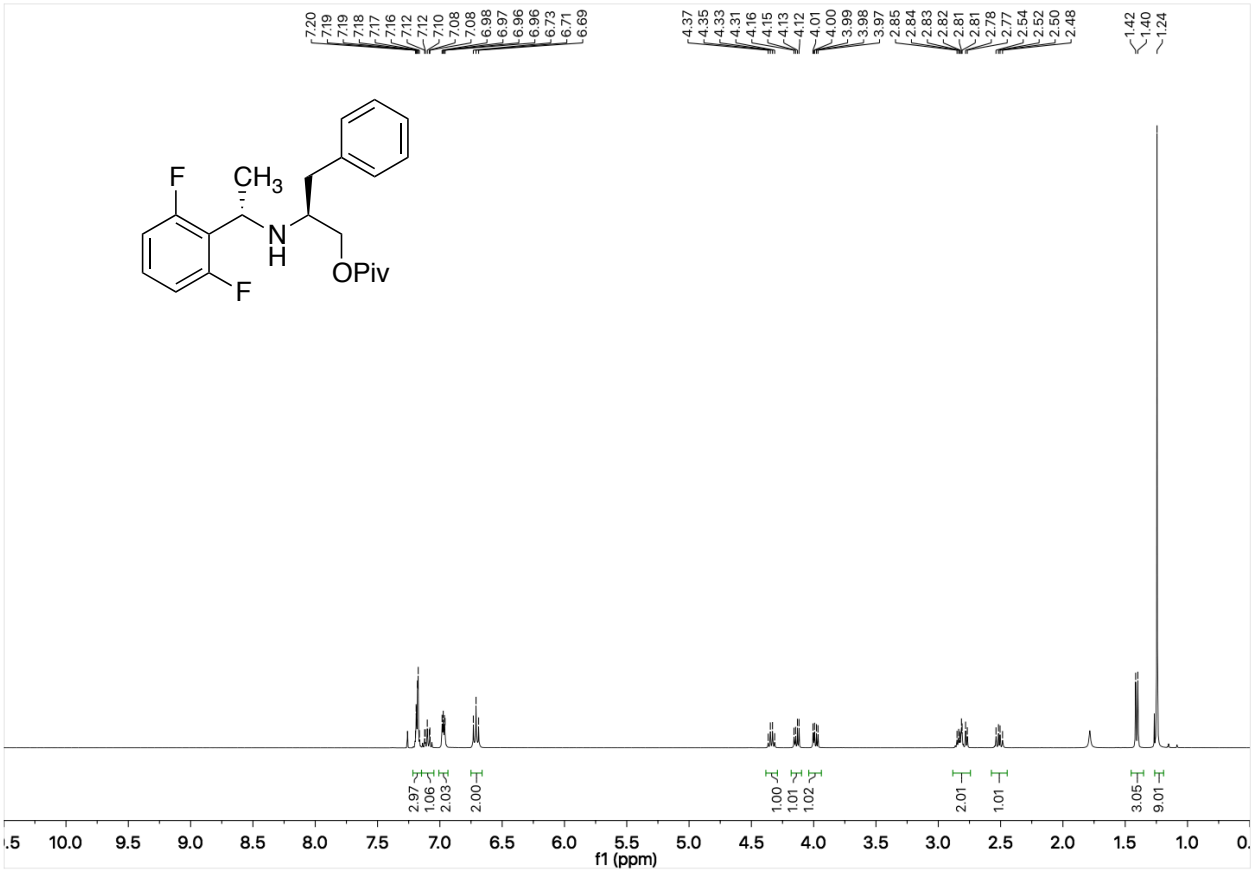


^{13}C NMR ($CDCl_3$, 100 MHz)

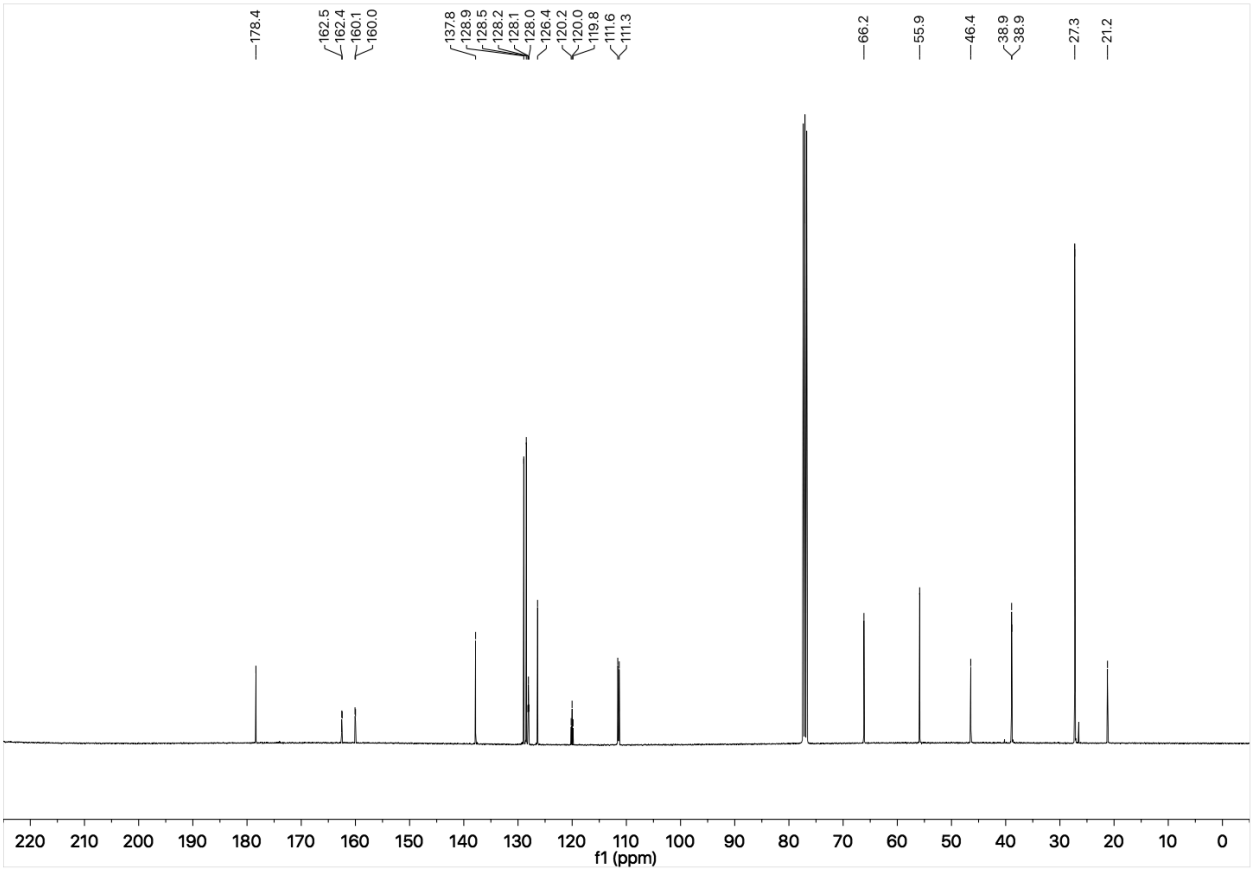


(S)-2-(((S)-1-(2,6-difluorophenyl)ethyl)amino)-4-methylpentyl pivalate (**261**)

^{1}H NMR ($CDCl_3$, 400 MHz)

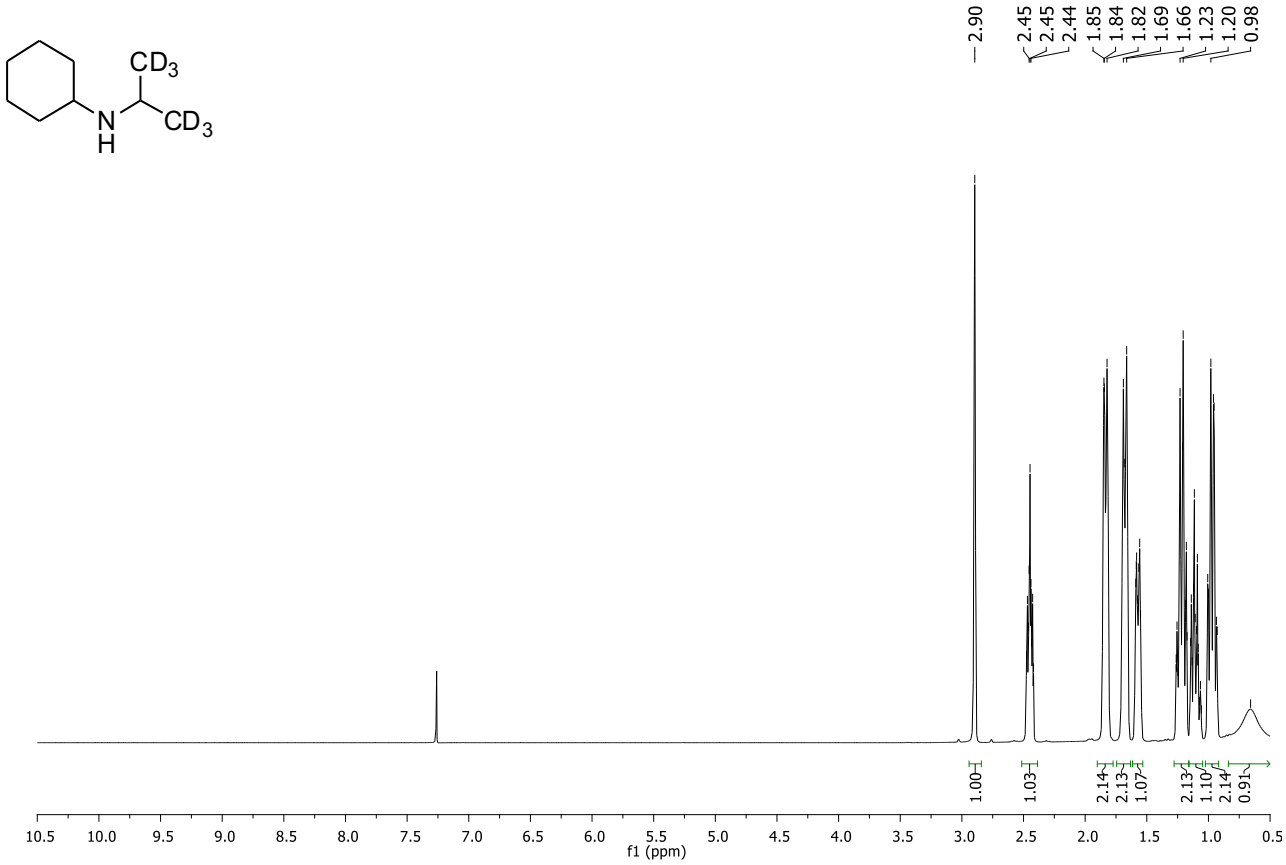


^{13}C NMR ($CDCl_3$, 100 MHz)

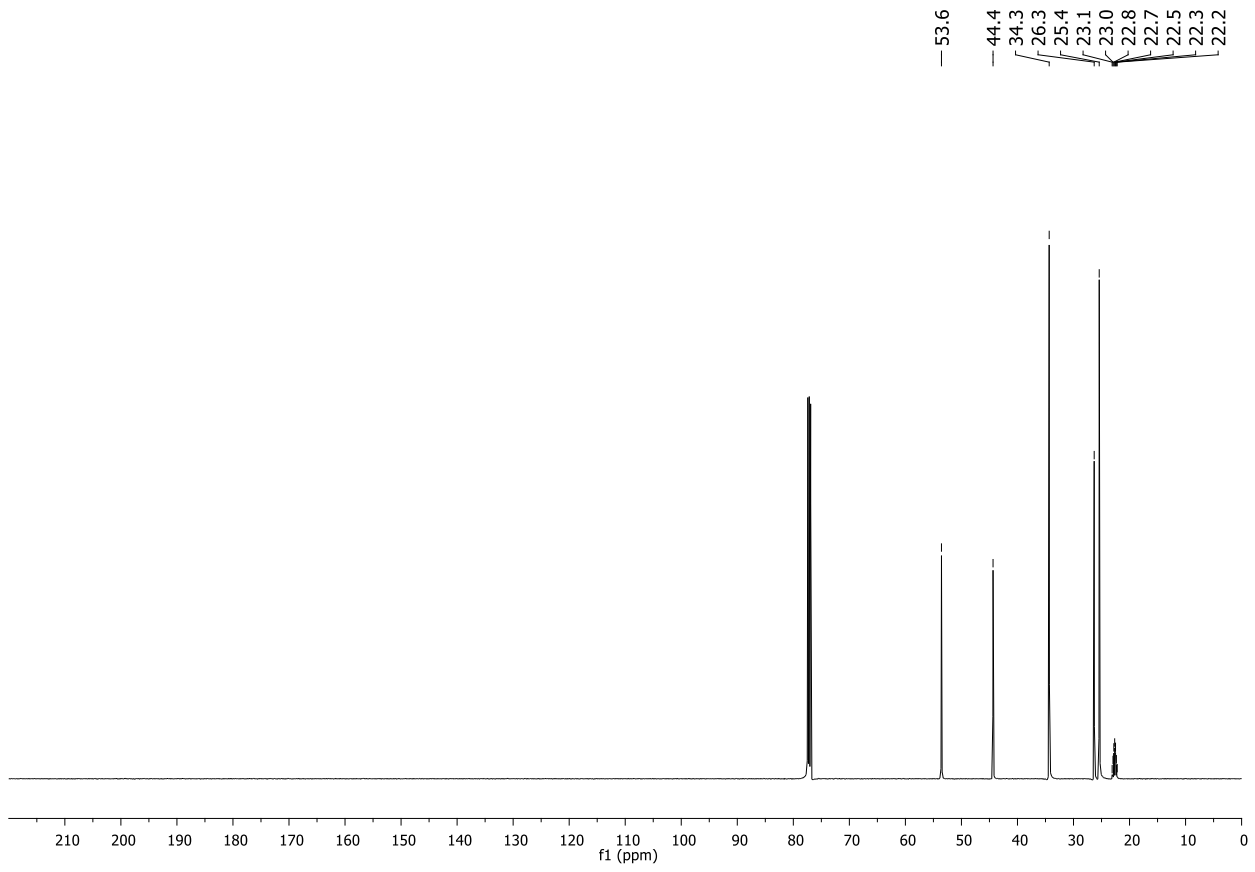


1,1,1,3,3,3-d^6-N-Isopropylcyclohexanamine (**d^6-197**)

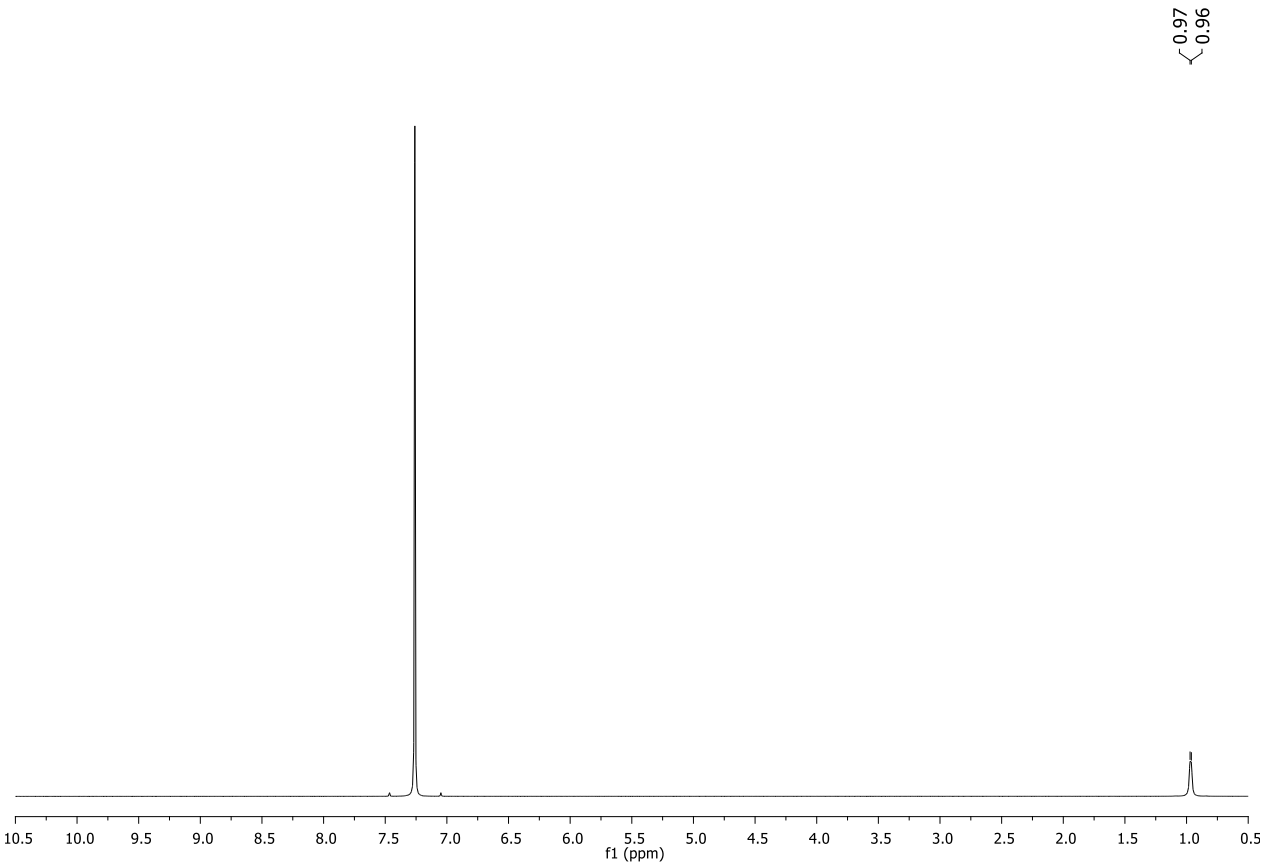
^{1}H NMR ($CDCl_3$, 500 MHz)



^{13}C NMR ($CDCl_3$, 126 MHz)



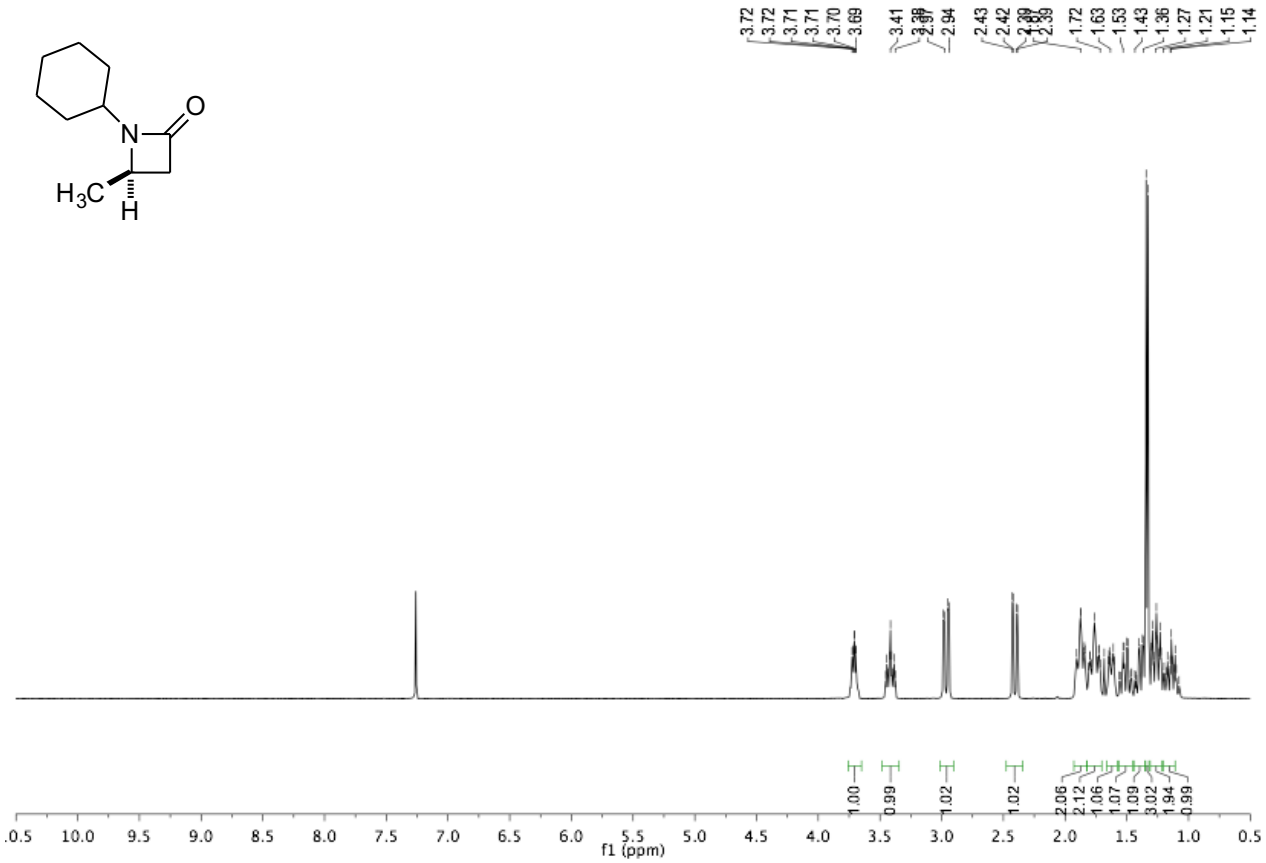
^{2}H NMR ($CDCl_3$, 77 MHz)



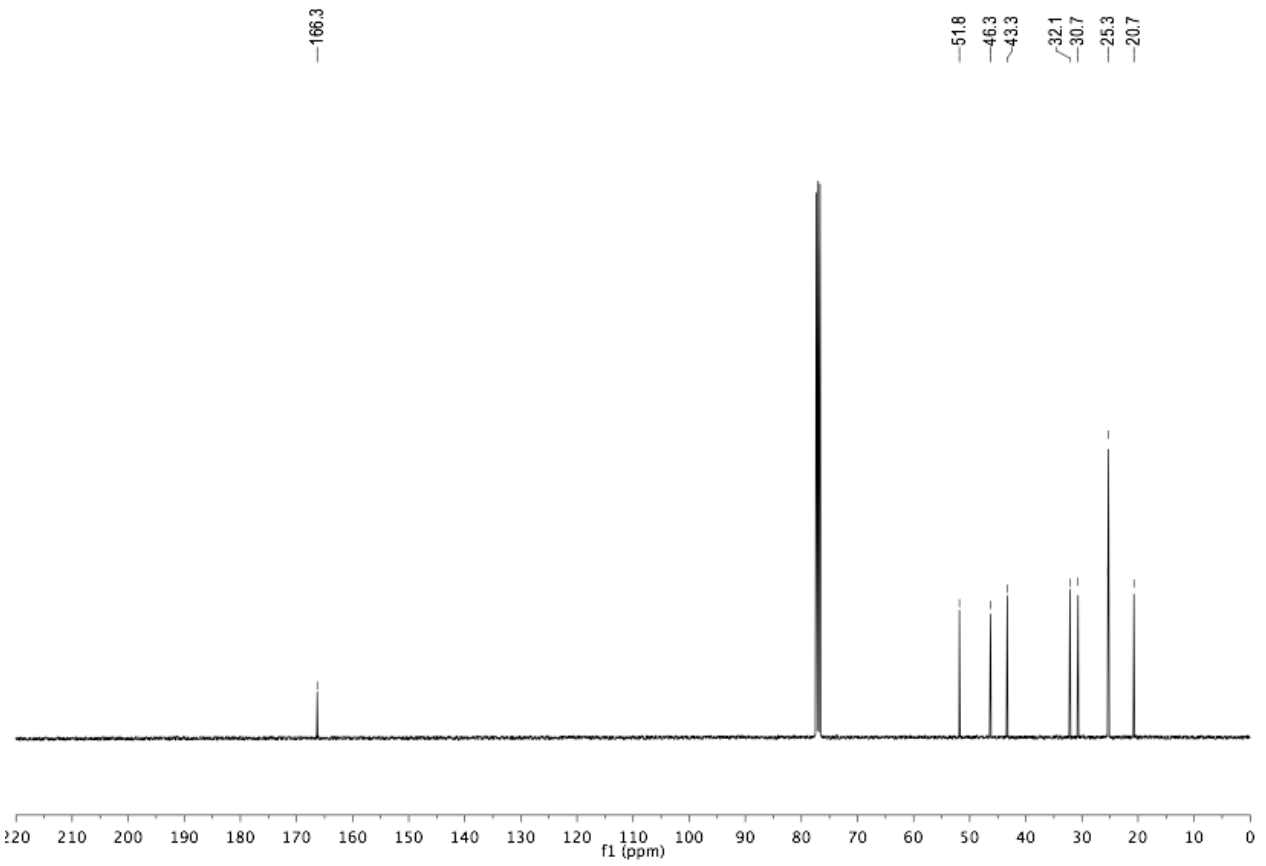
Carbonylation products

1-Cyclohexyl-4-methylazetidin-2-one (**196**)

^{1}H NMR ($CDCl_3$, 400 MHz)

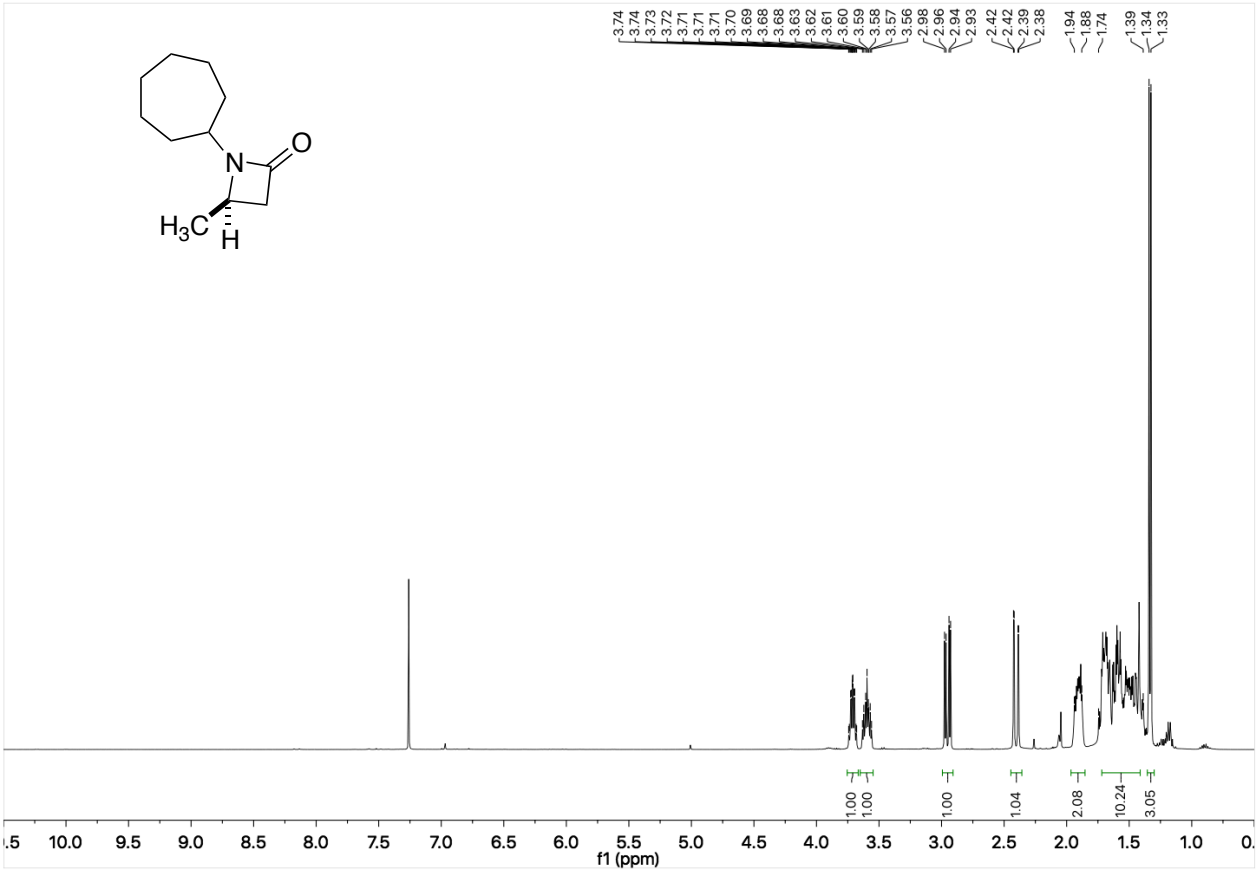


^{13}C NMR ($CDCl_3$, 100 MHz)

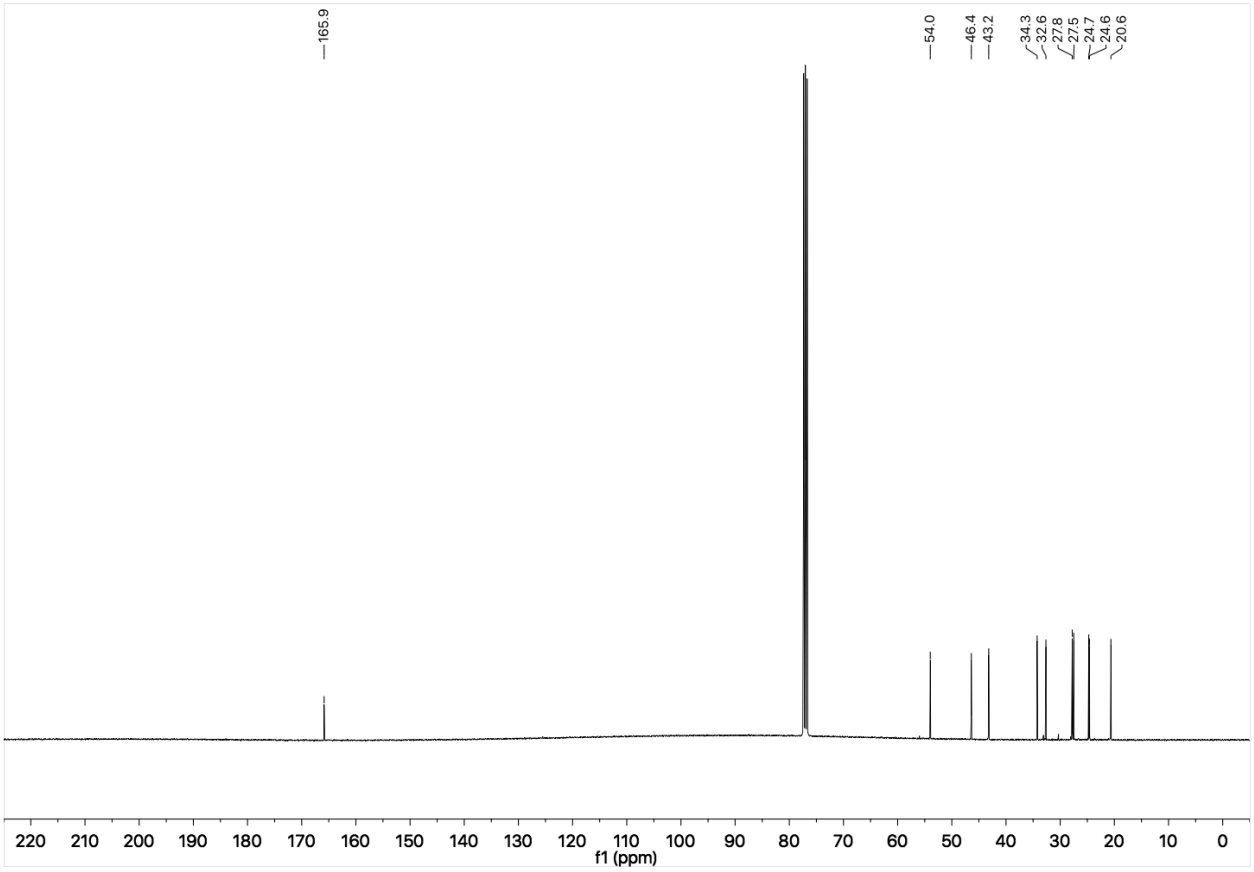


1-Cycloheptyl-4-methylazetidin-2-one (**202**)

^{1}H NMR ($CDCl_3$, 400 MHz)

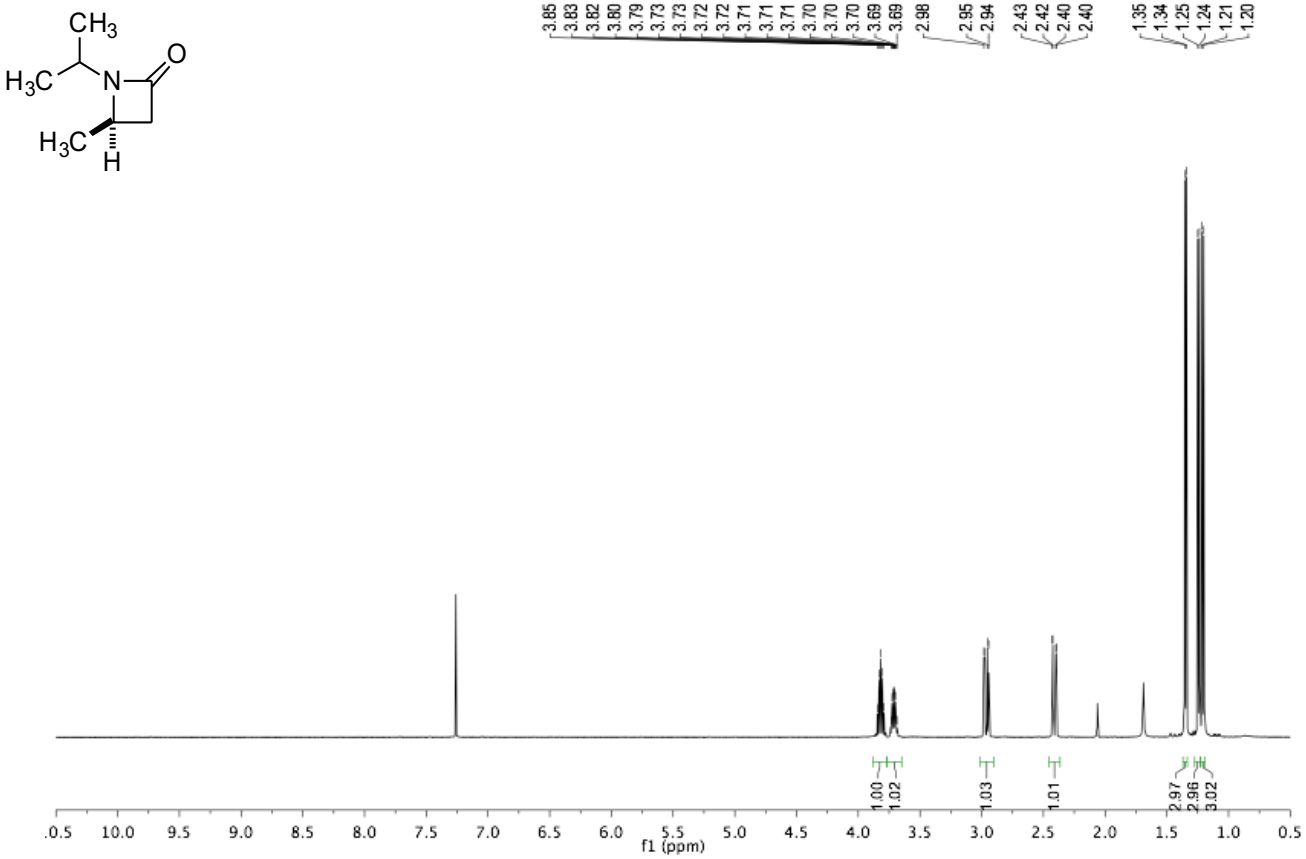


^{13}C NMR ($CDCl_3$, 100 MHz)

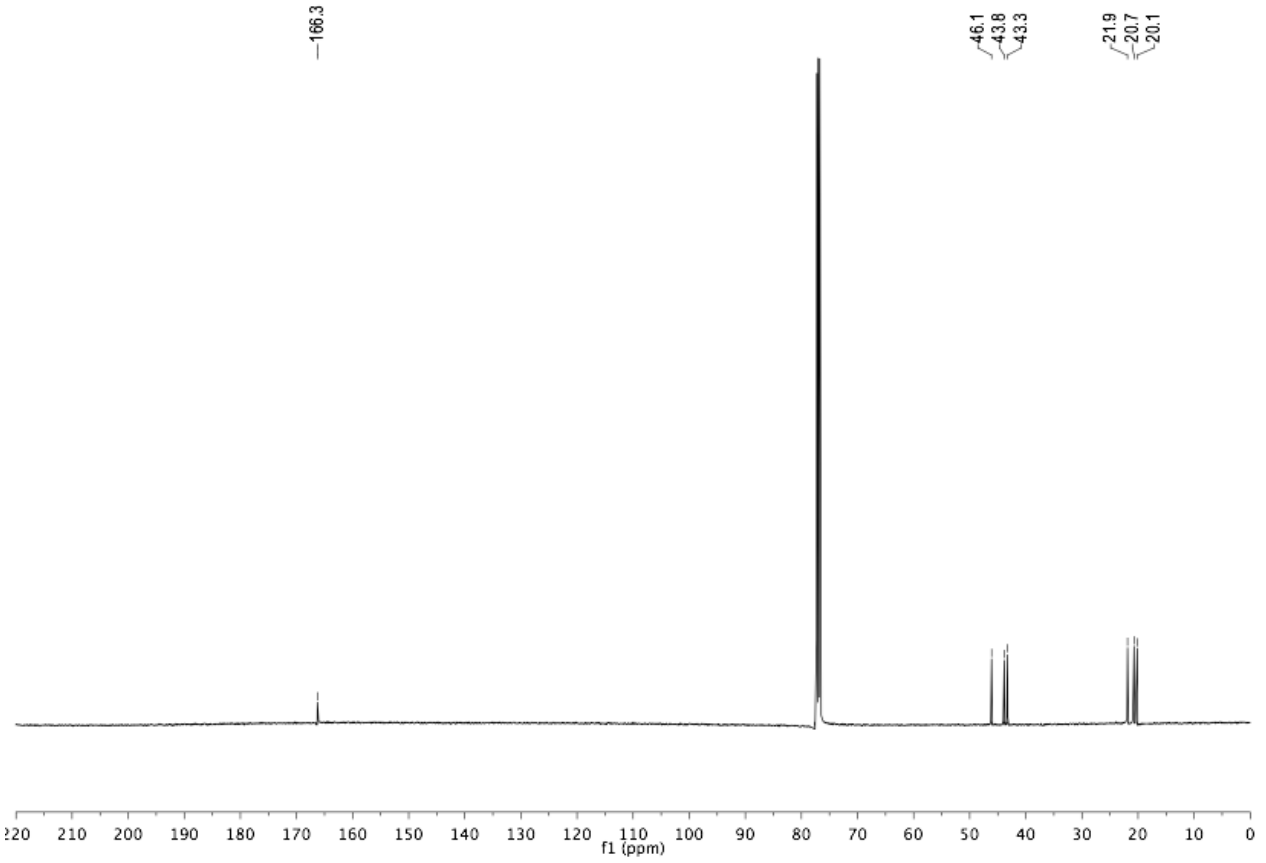


1-Isopropyl-4-methylazetidin-2-one (**204**)

^{1}H NMR ($CDCl_3$, 400 MHz)

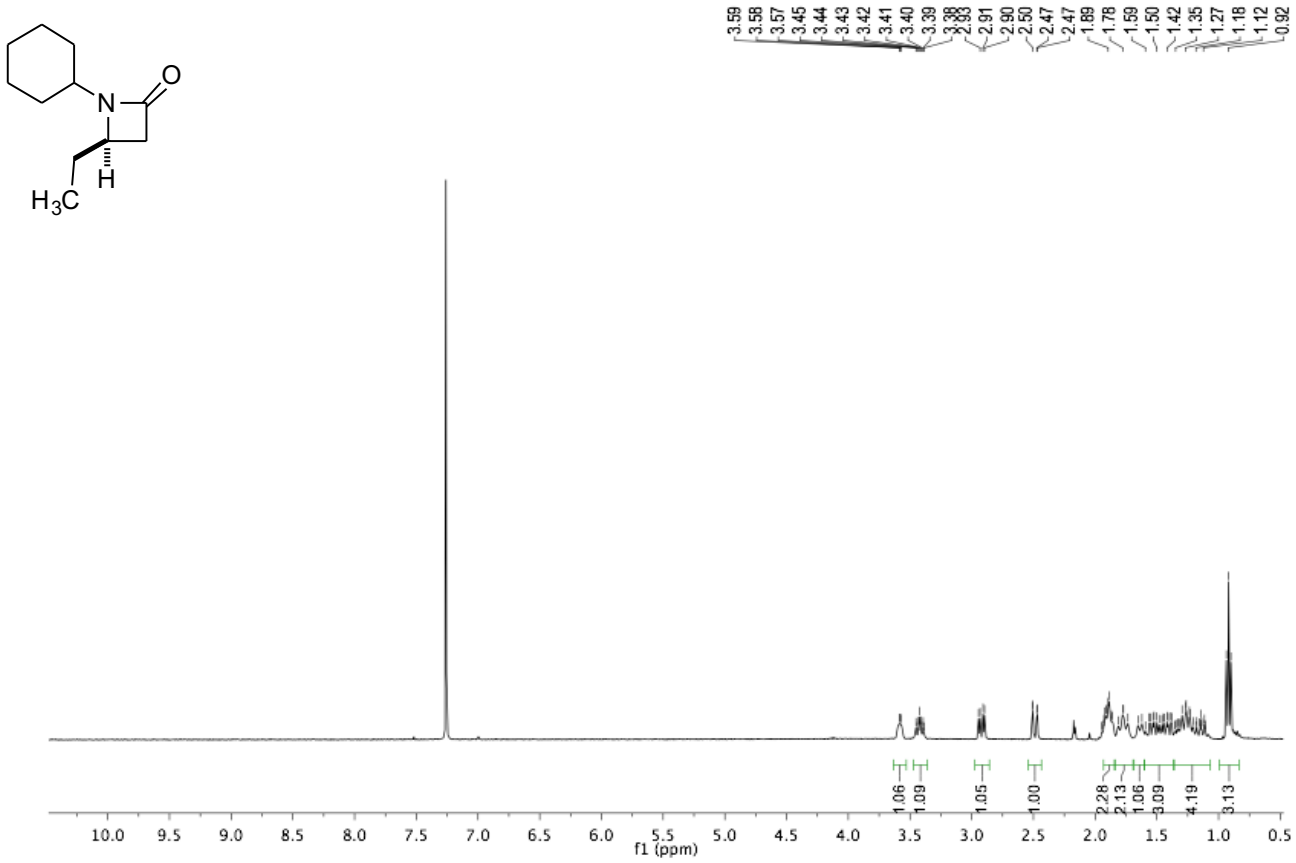


^{13}C NMR ($CDCl_3$, 100 MHz)

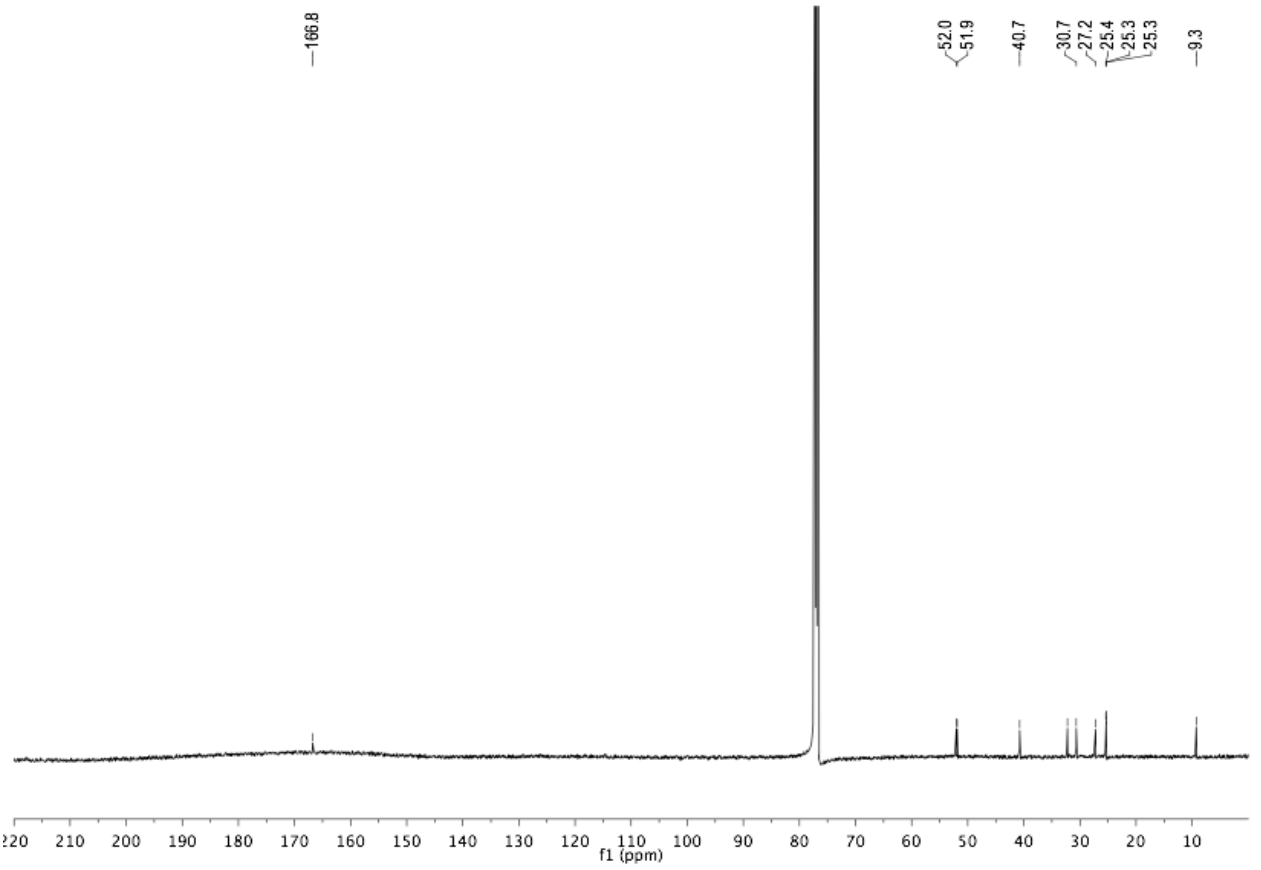


1-Cyclohexyl-4-ethylazetidin-2-one (**205**)

^{1}H NMR ($CDCl_3$, 400 MHz)

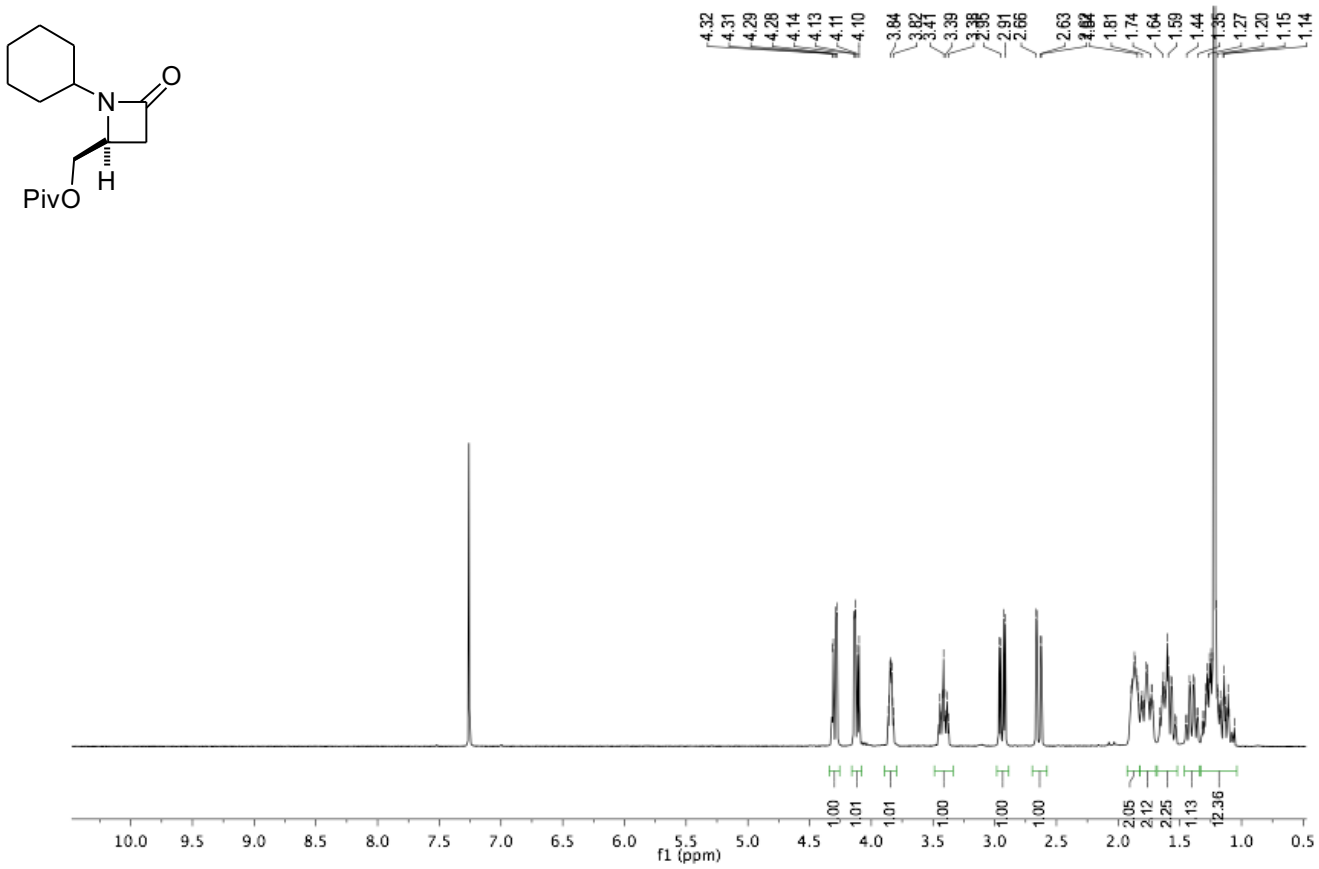


^{13}C NMR ($CDCl_3$, 100 MHz)

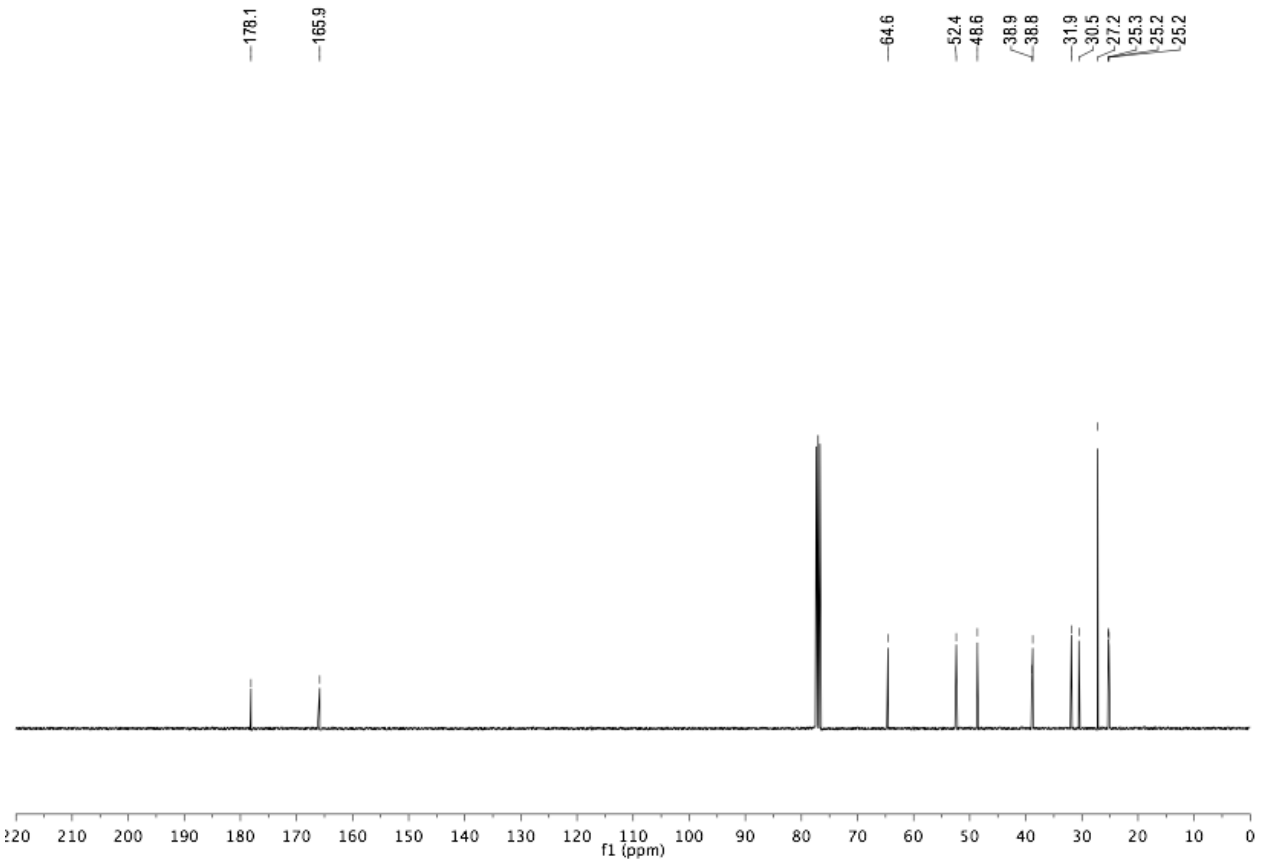


(1-Cyclohexyl-4-oxoazetidin-2-yl)methyl pivalate (**206**)

^{1}H NMR ($CDCl_3$, 400 MHz)

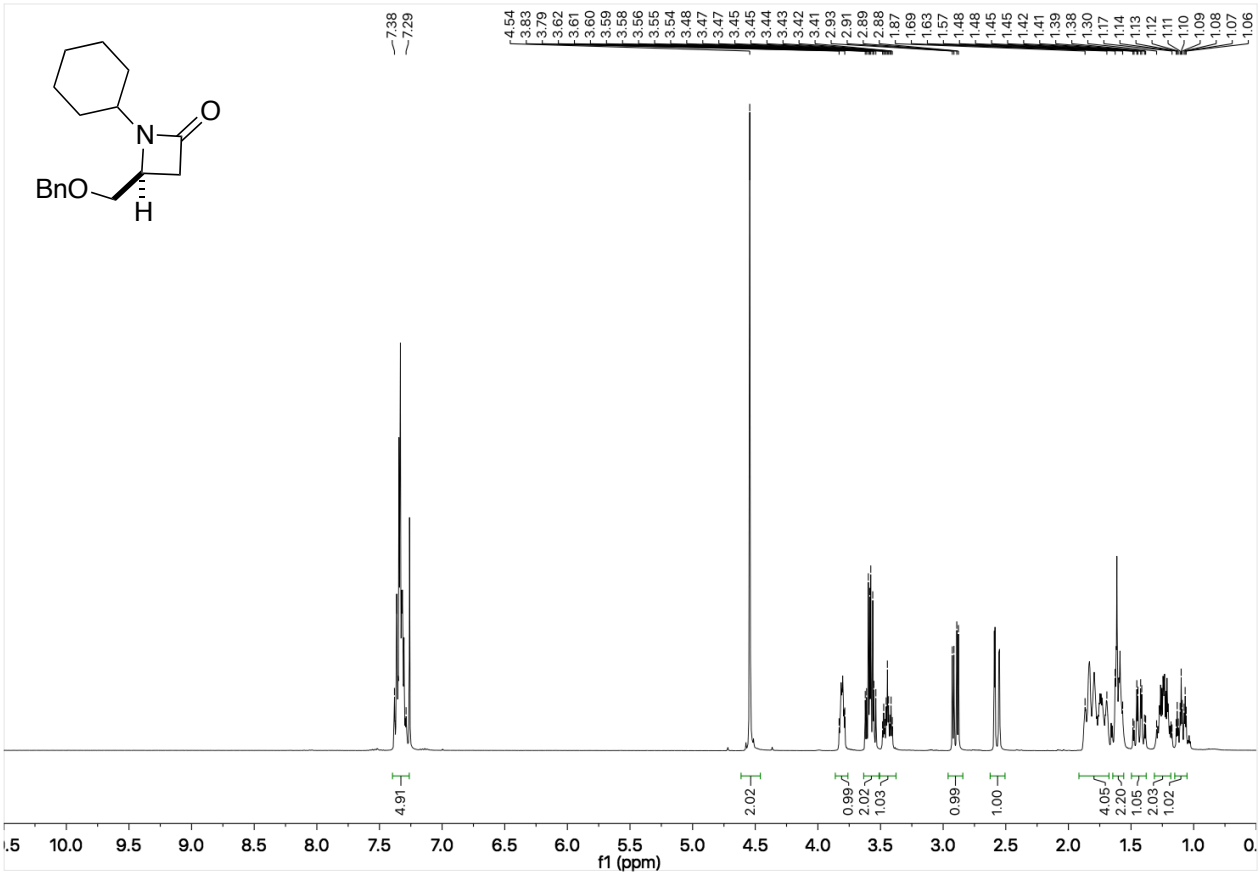


^{13}C NMR ($CDCl_3$, 100 MHz)

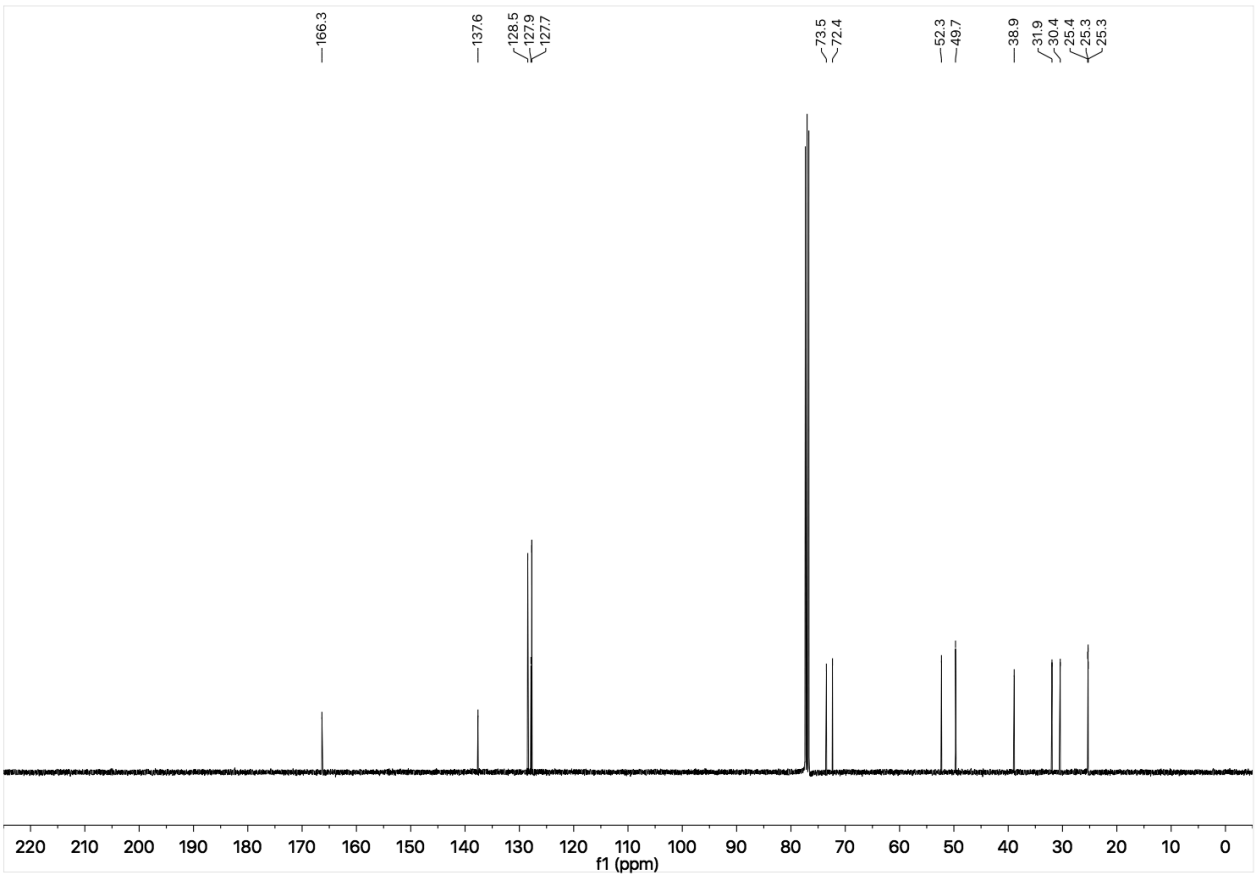


4-((Benzyloxy)methyl)-1-cyclohexylazetidin-2-one (**208**)

^{1}H NMR ($CDCl_3$, 400 MHz)

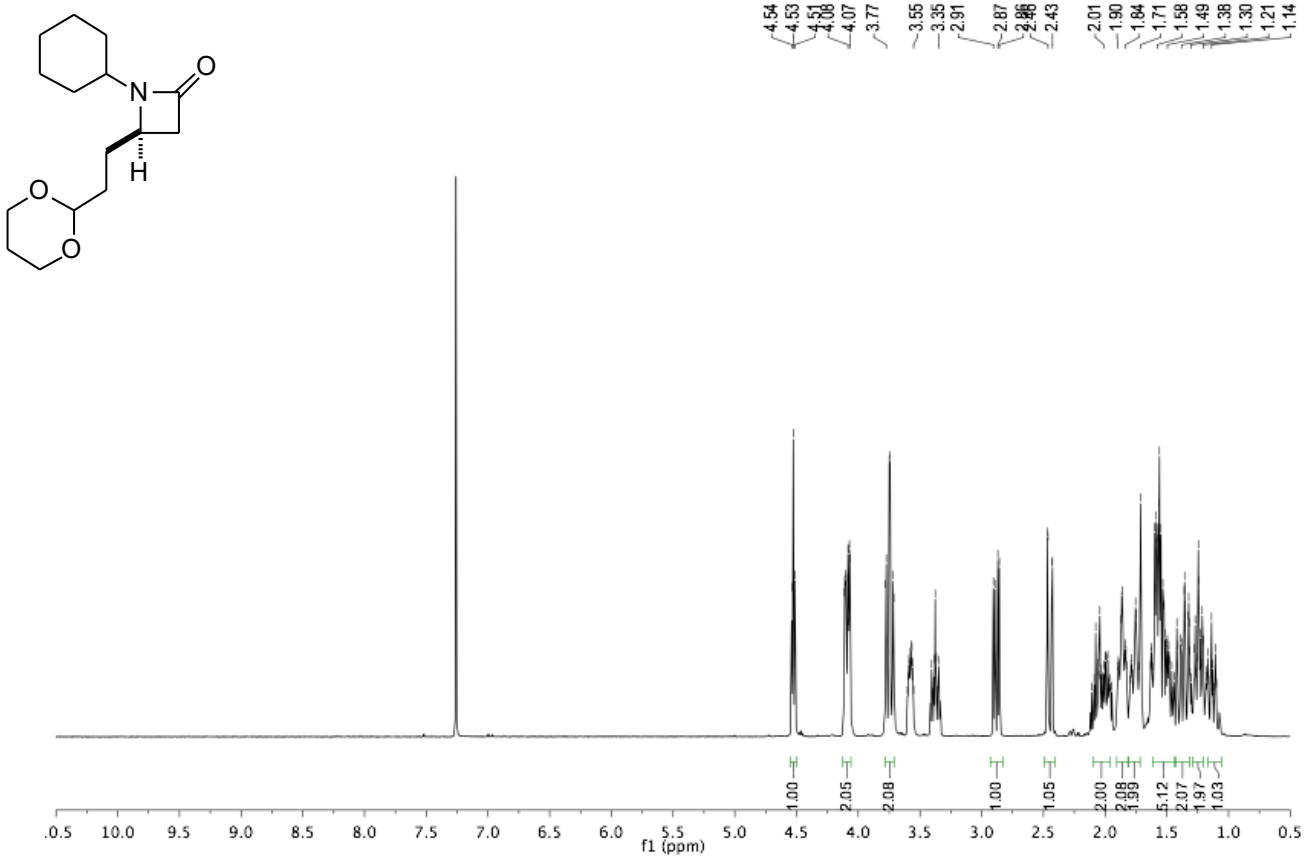


^{13}C NMR ($CDCl_3$, 100 MHz)

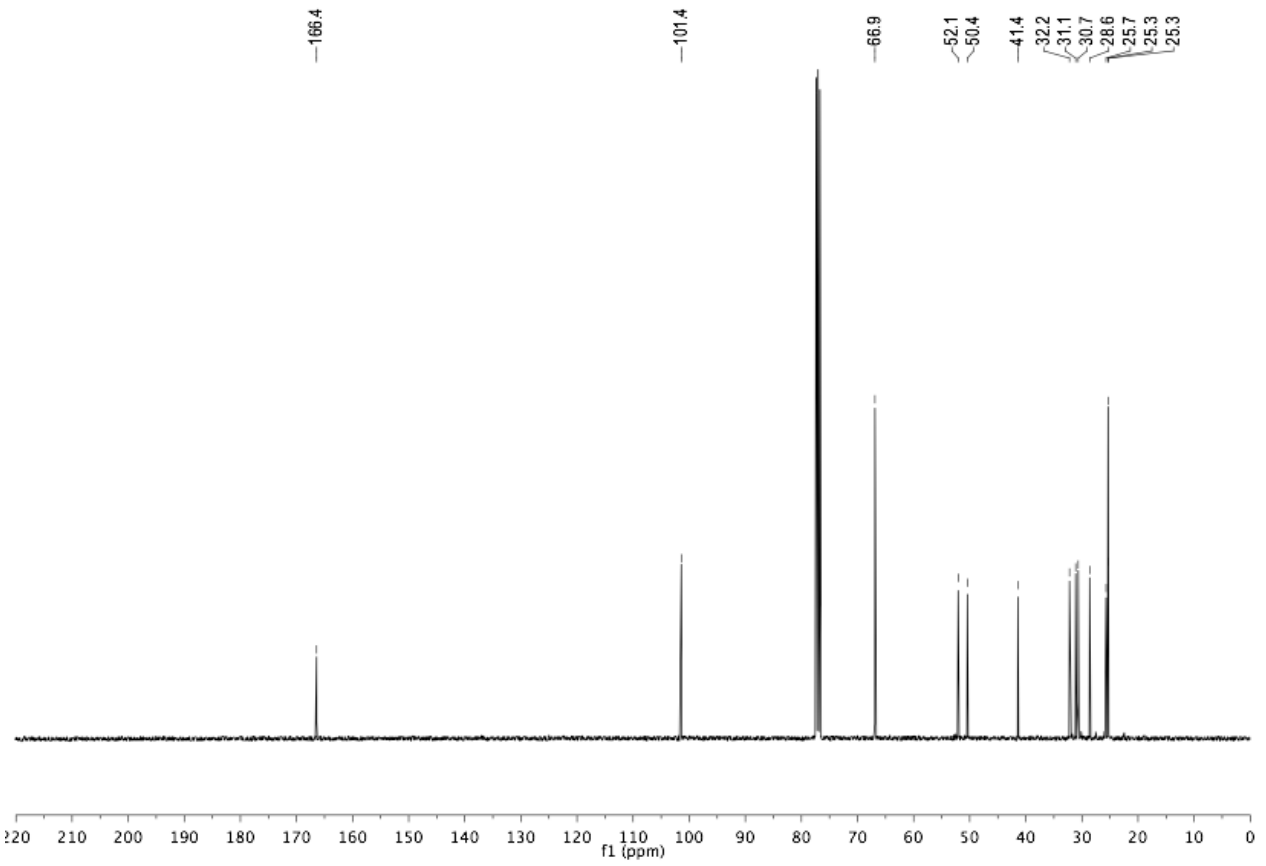


4-(2-(1,3-Dioxan-2-yl)ethyl)-1-cyclohexylazetidin-2-one (**213**)

^{1}H NMR ($CDCl_3$, 400 MHz)

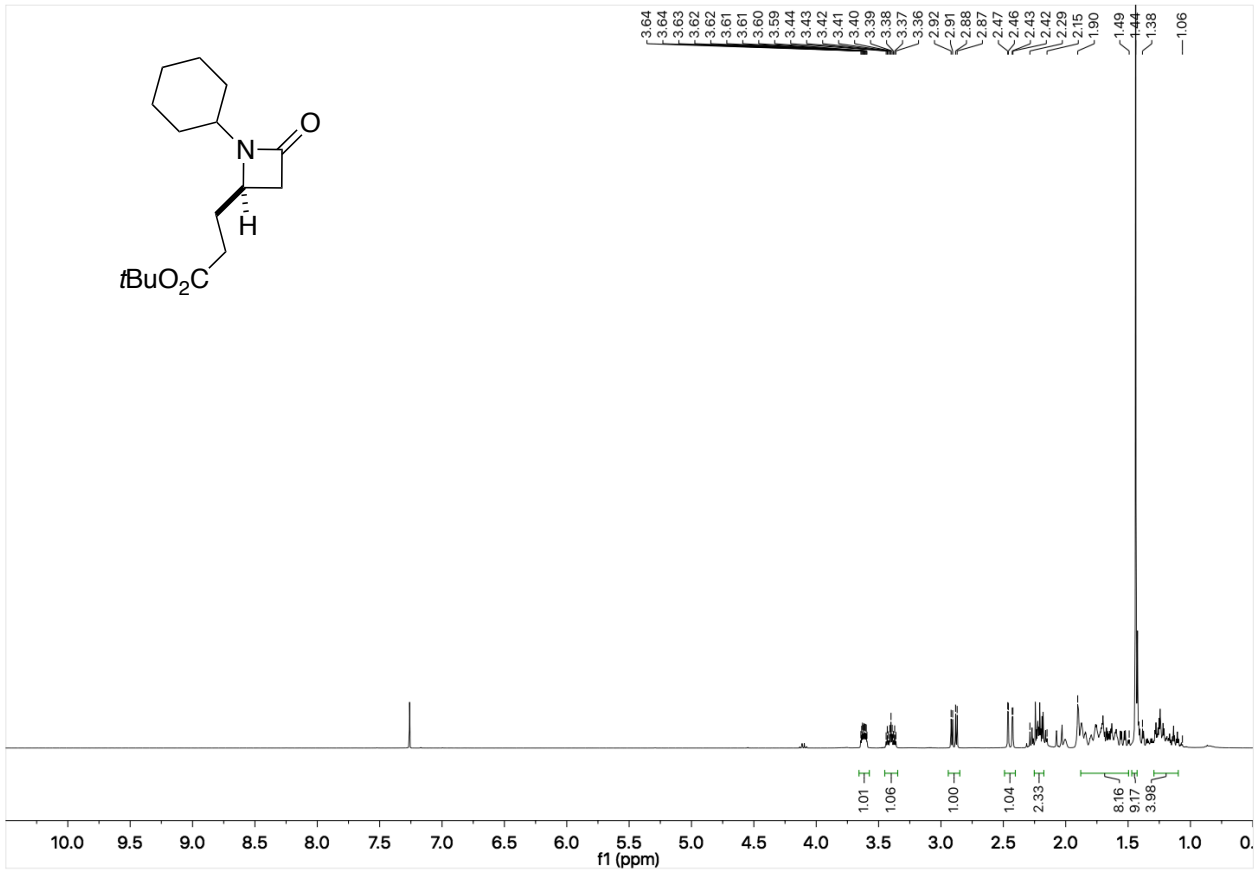


^{13}C NMR ($CDCl_3$, 100 MHz)

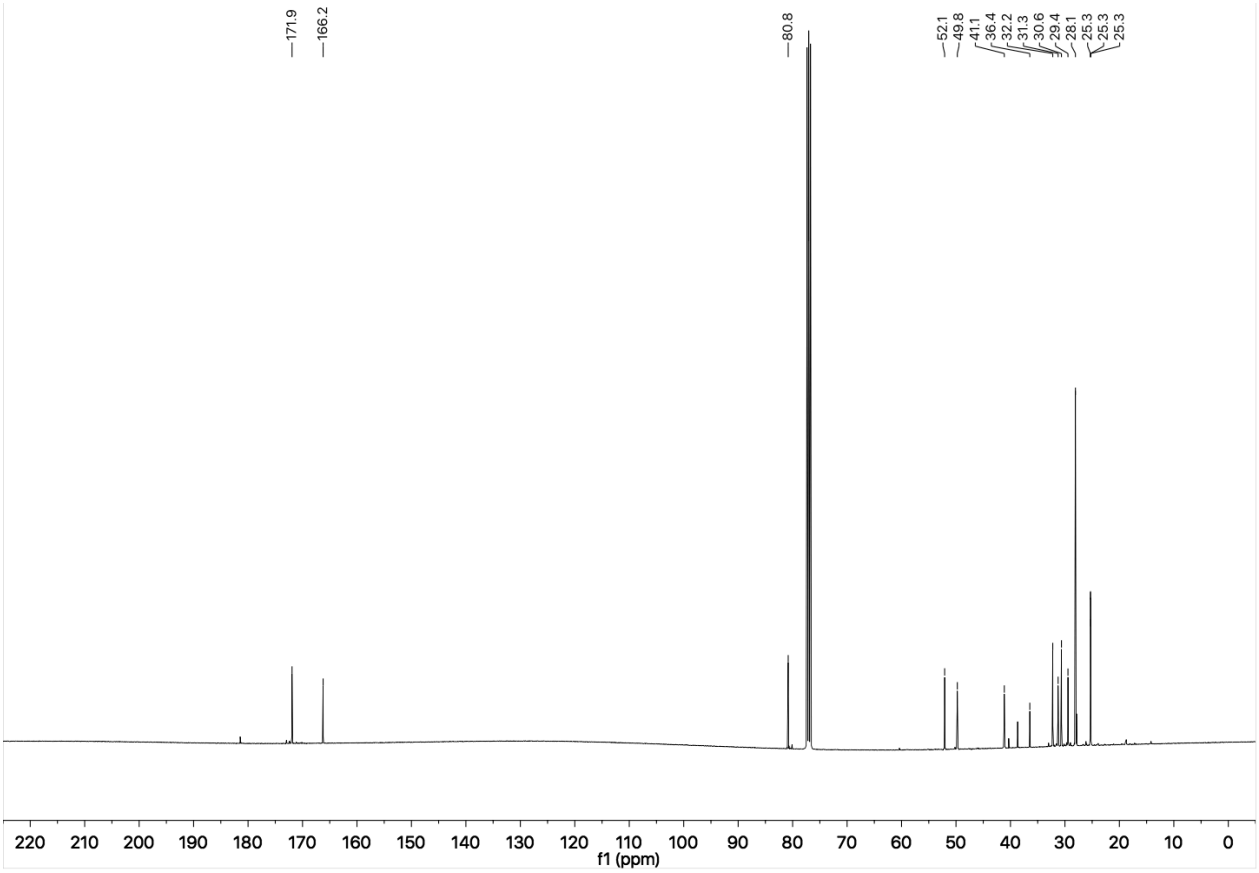


tert-Butyl 3-(1-cyclohexyl-4-oxoazetidin-2-yl)propanoate (**212**)

^{1}H NMR ($CDCl_3$, 400 MHz)

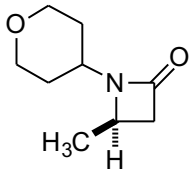


^{13}C NMR ($CDCl_3$, 100 MHz)

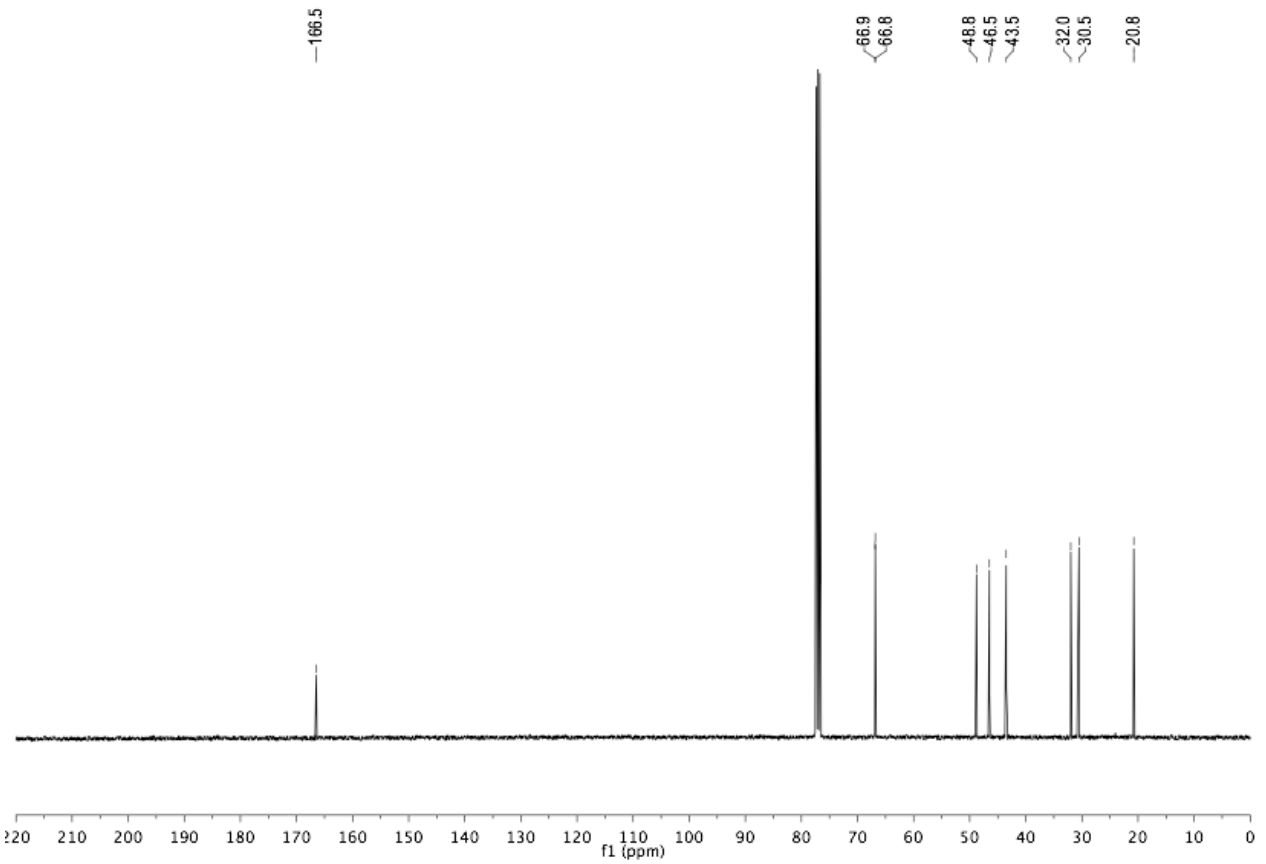


4-Methyl-1-(tetrahydro-2H-pyran-4-yl)azetidin-2-one (**214**)

^{1}H NMR ($CDCl_3$, 400 MHz)

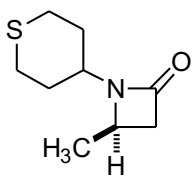


^{13}C NMR ($CDCl_3$, 100 MHz)

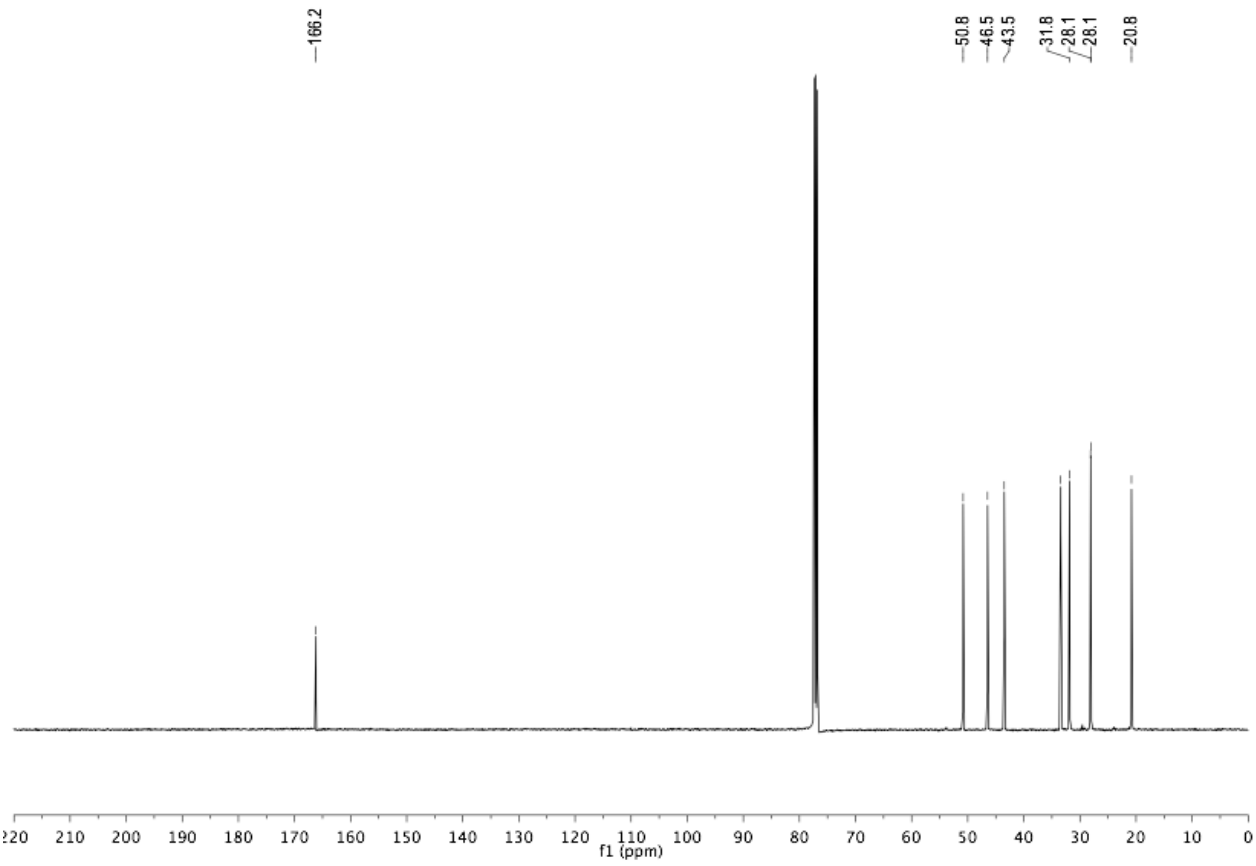


4-Methyl-1-(tetrahydro-2H-thiopyran-4-yl)azetidin-2-one (**215**)

^{1}H NMR ($CDCl_3$, 400 MHz)

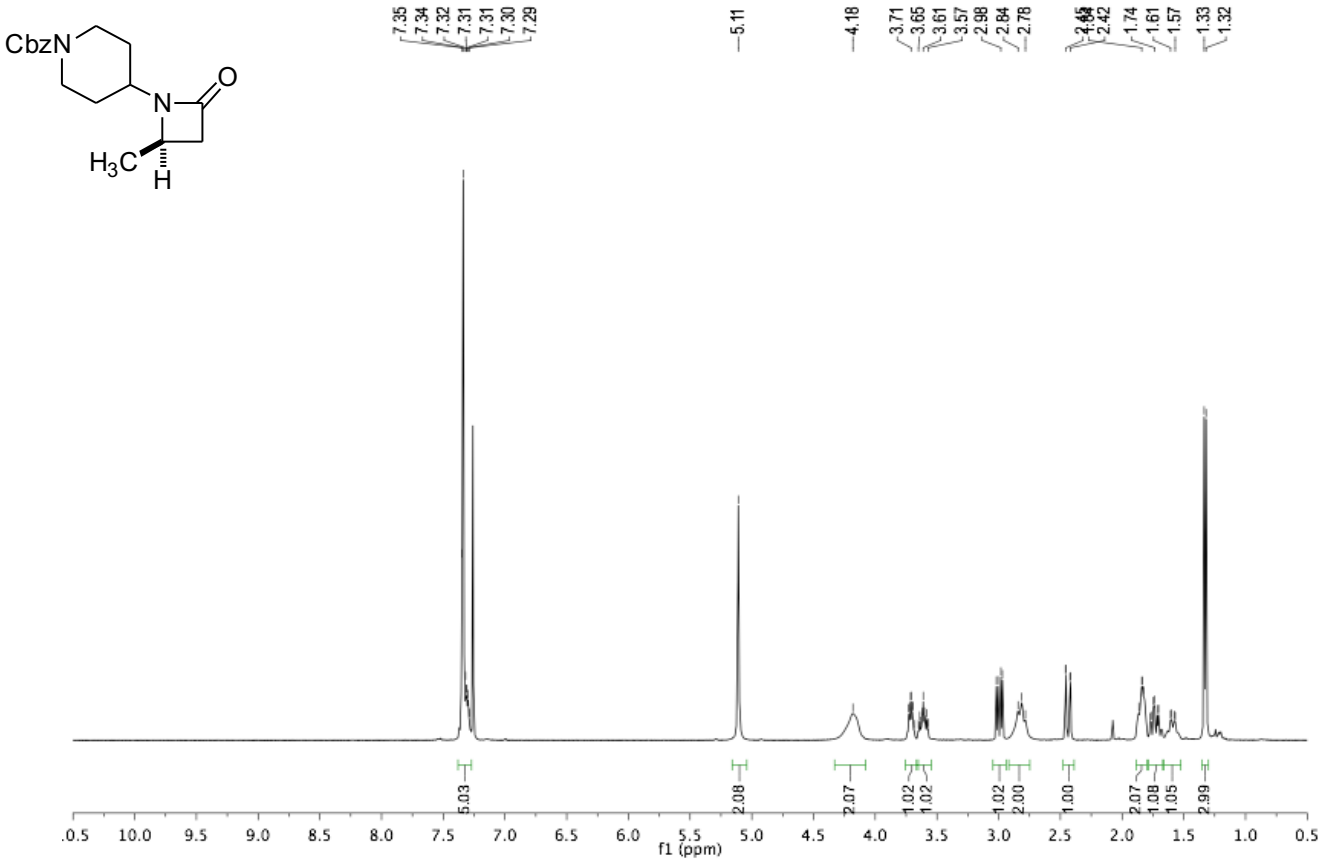


^{13}C NMR ($CDCl_3$, 100 MHz)

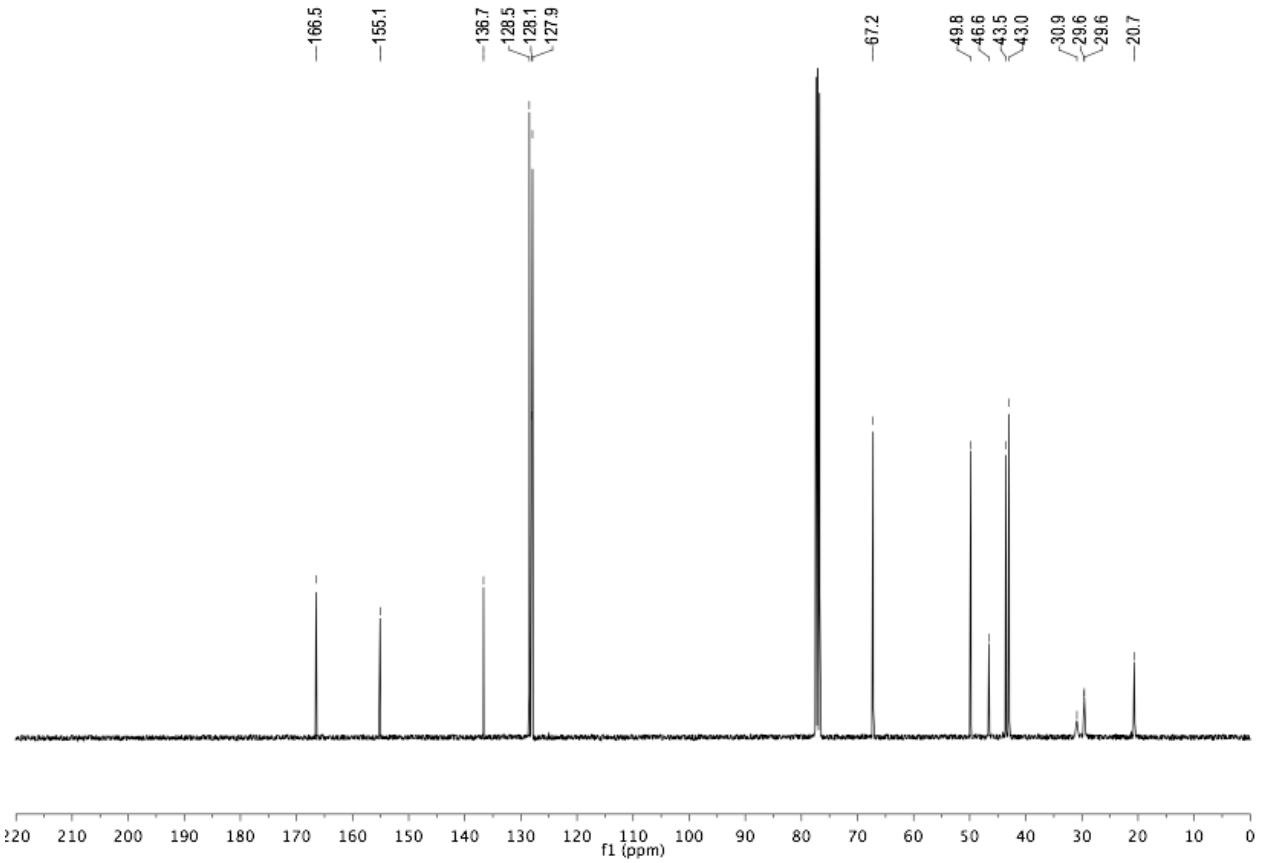


Benzyl 4-(2-methyl-4-oxoazetidin-1-yl)piperidine-1-carboxylate (**198**)

^{1}H NMR ($CDCl_3$, 400 MHz)

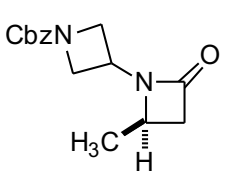


^{13}C NMR ($CDCl_3$, 100 MHz)

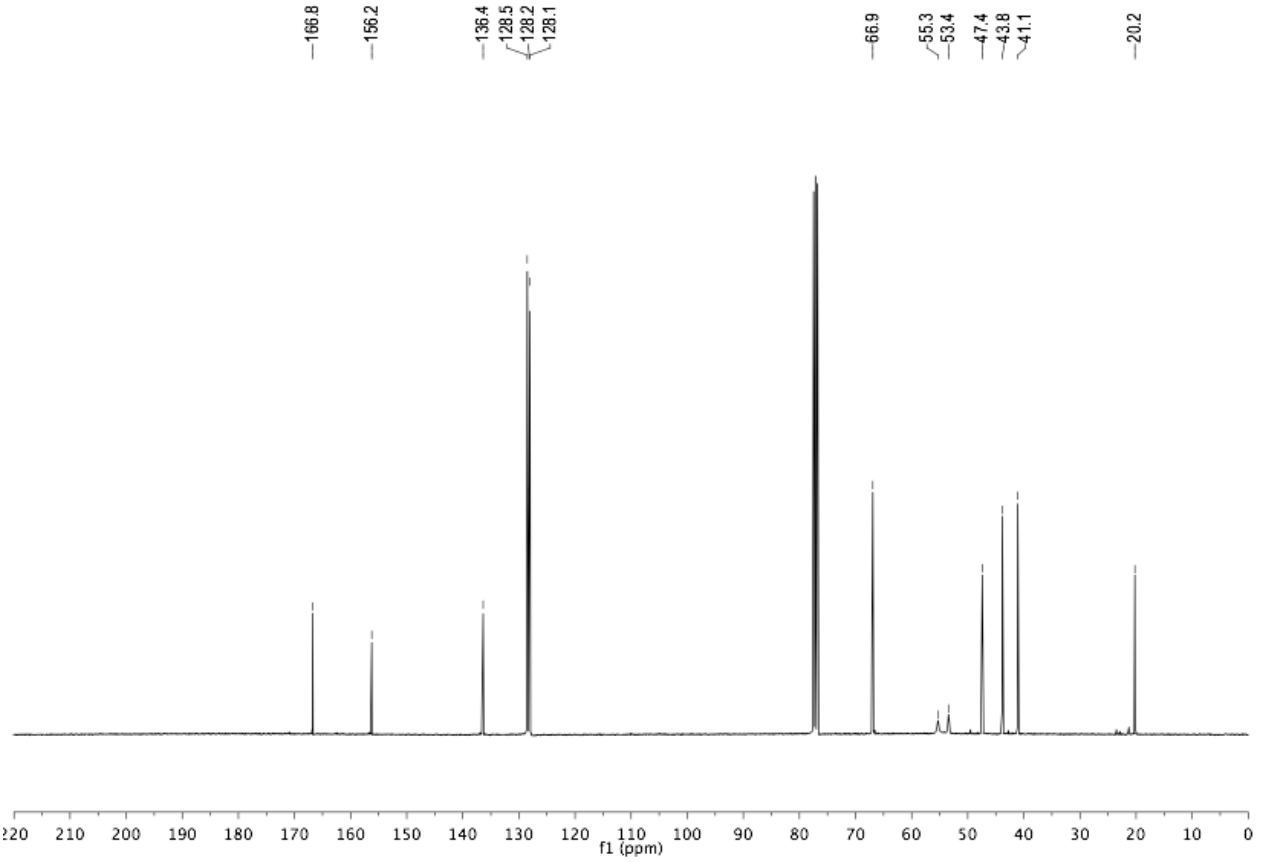


Benzyl 2-methyl-4-oxo-[1,3'-biazetidine]-1'-carboxylate (**216**)

^{1}H NMR ($CDCl_3$, 400 MHz)

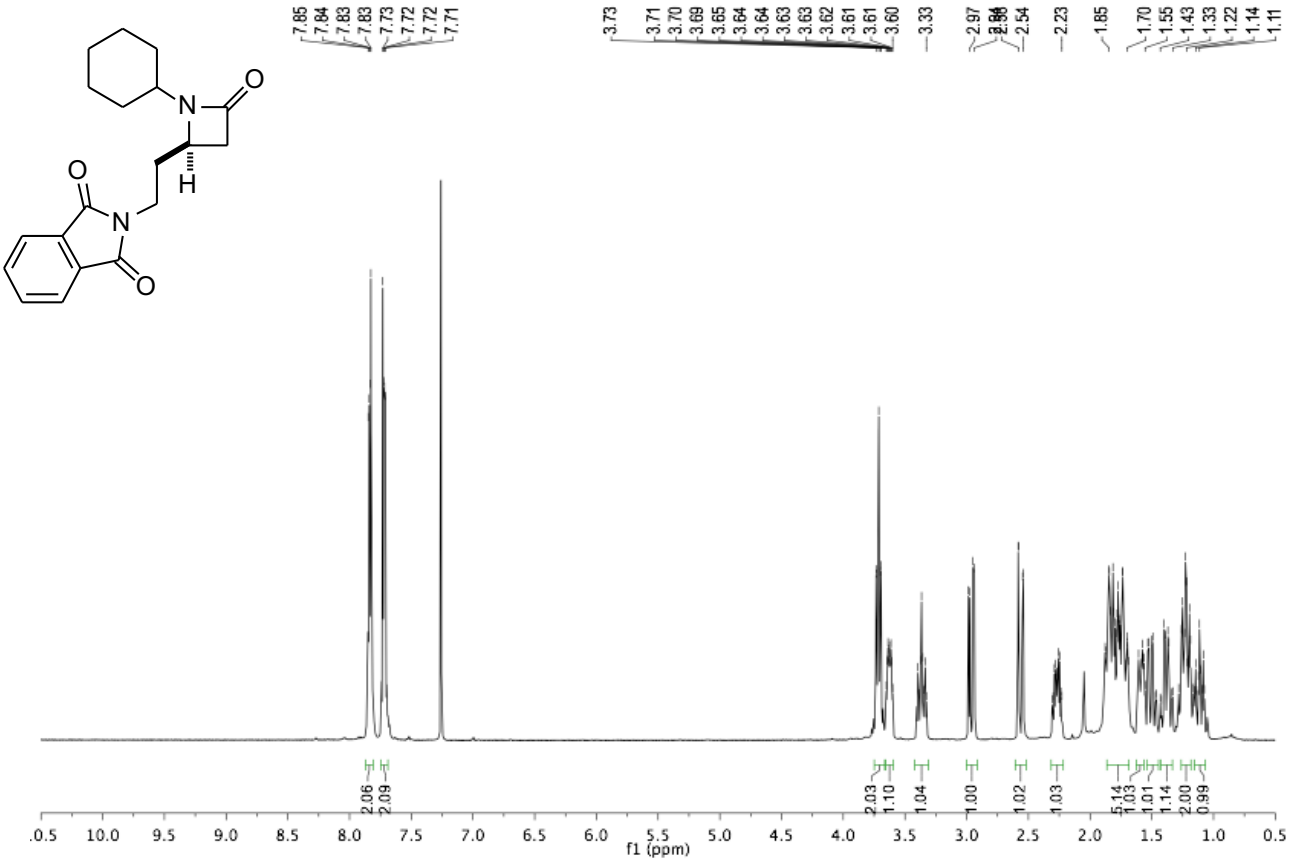


^{13}C NMR ($CDCl_3$, 100 MHz)

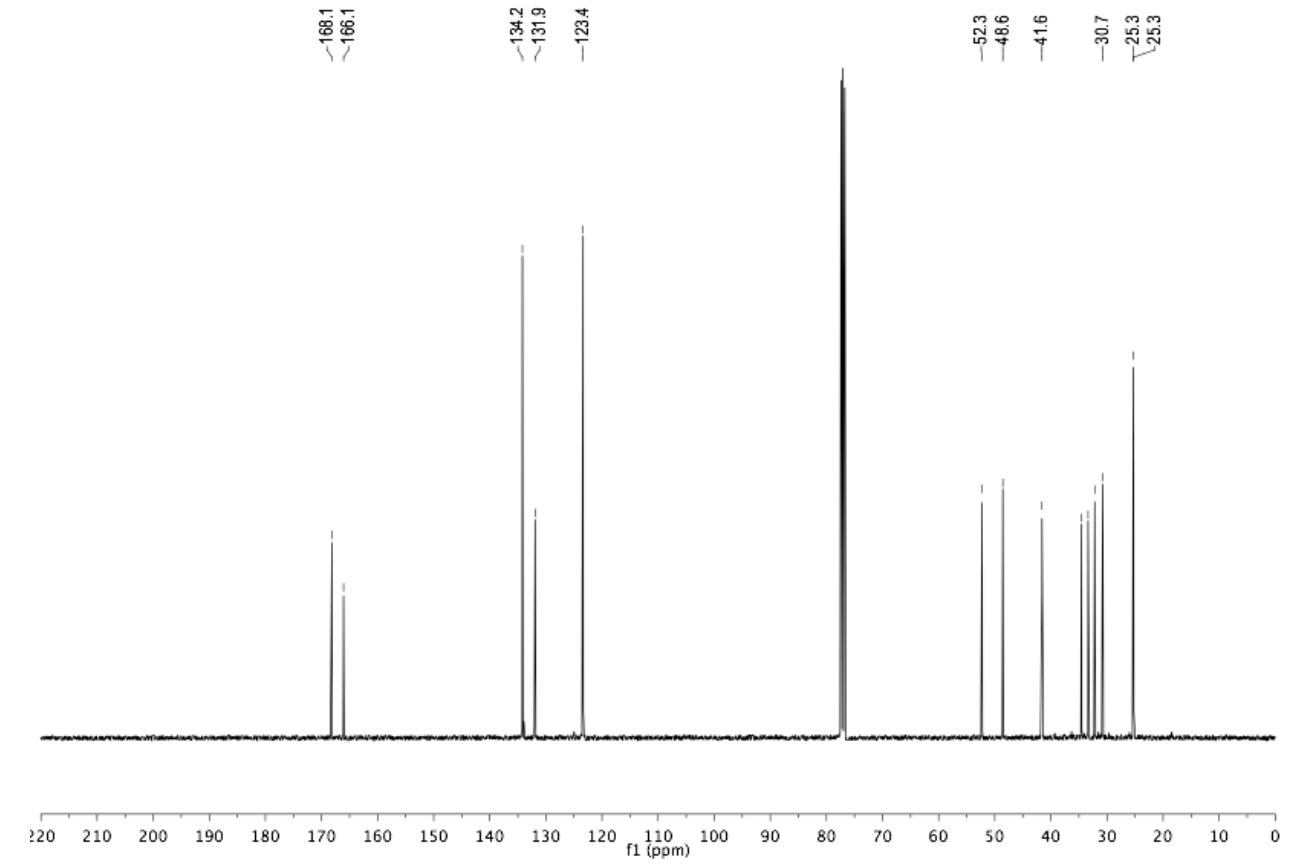


2-(2-(1-Cyclohexyl-4-oxoazetidin-2-yl)ethyl)isoindoline-1,3-dione (**199**)

^{1}H NMR ($CDCl_3$, 400 MHz)

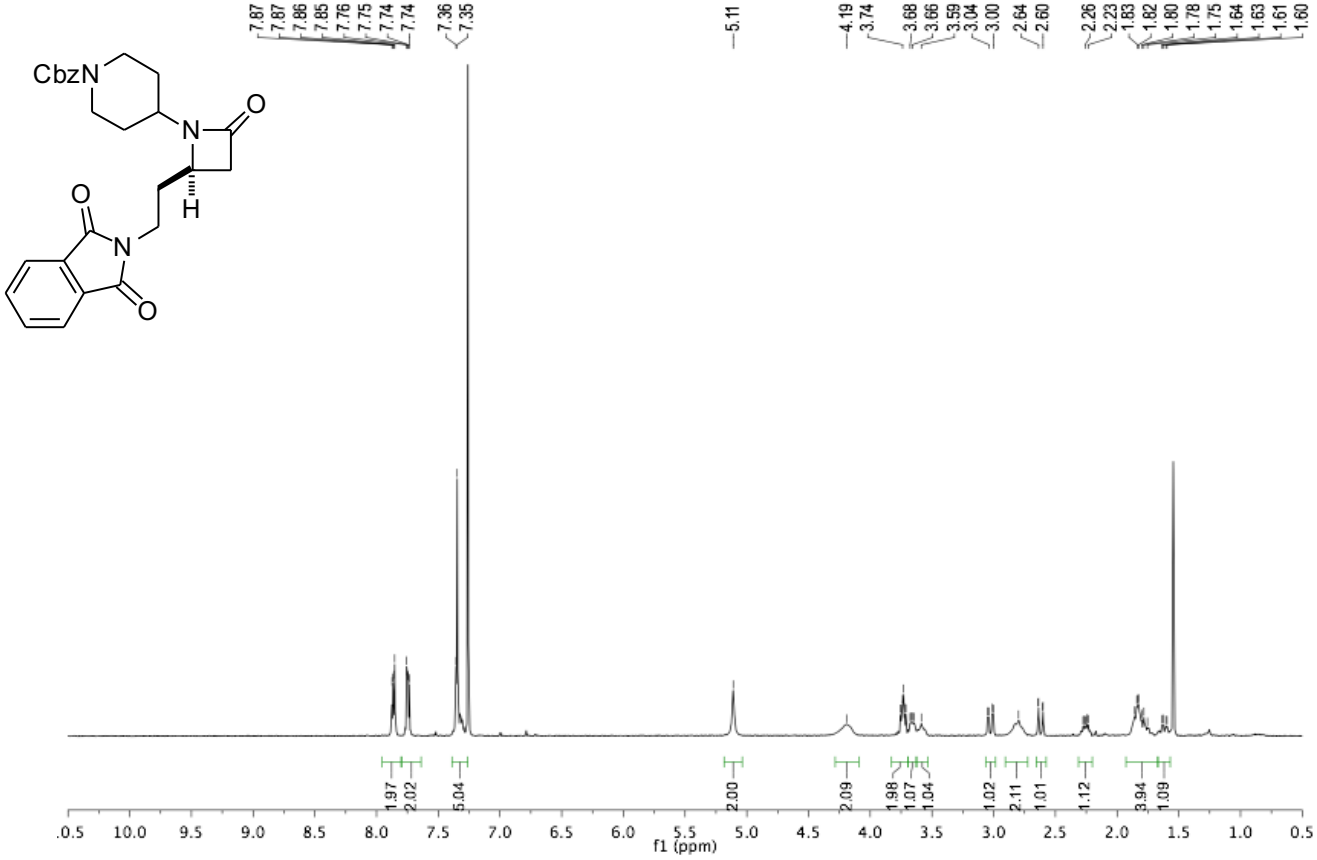


^{13}C NMR ($CDCl_3$, 100 MHz)

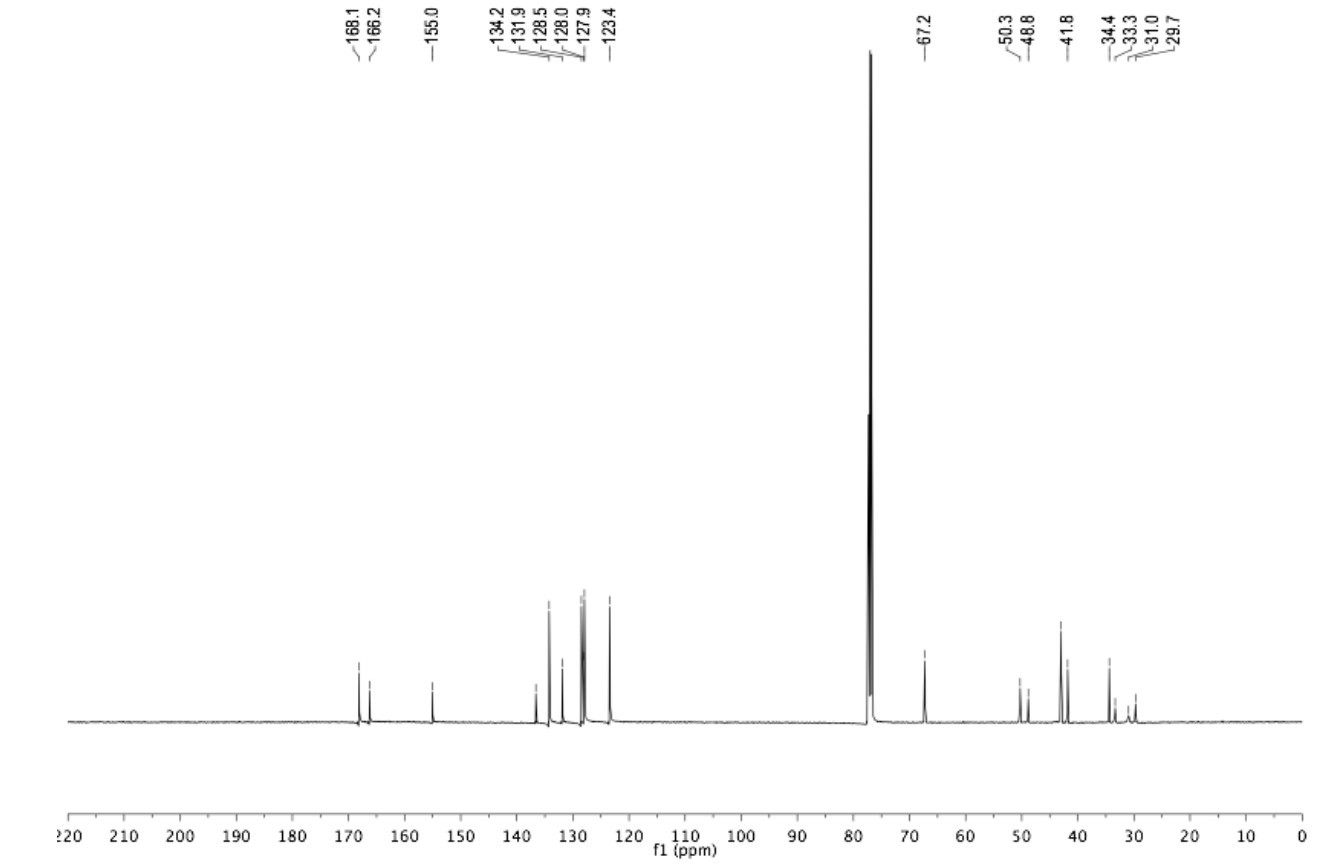


Benzyl 4-(2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-oxoazetidin-1-yl)piperidine-1-carboxylate **(217)**

^{1}H NMR ($CDCl_3$, 400 MHz)

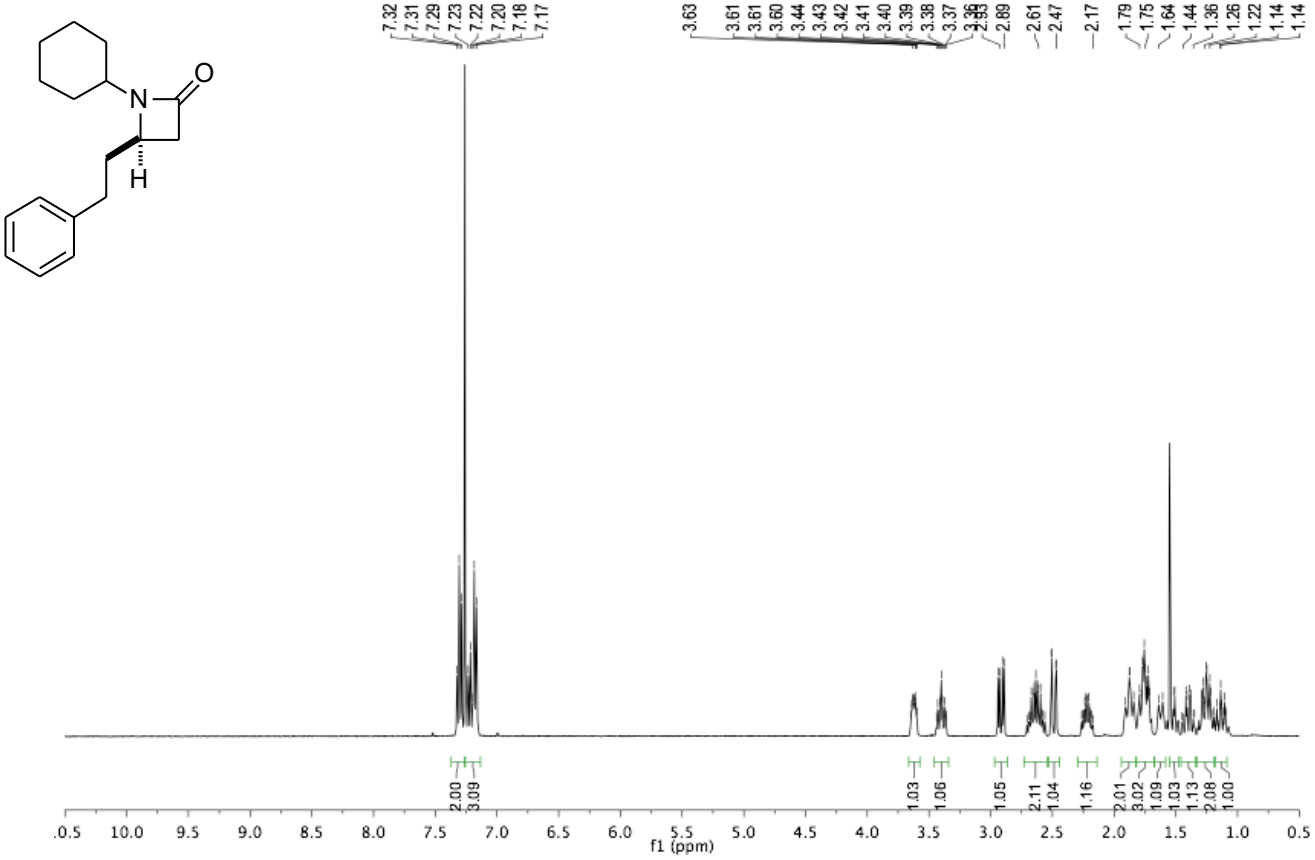


^{13}C NMR ($CDCl_3$, 100 MHz)

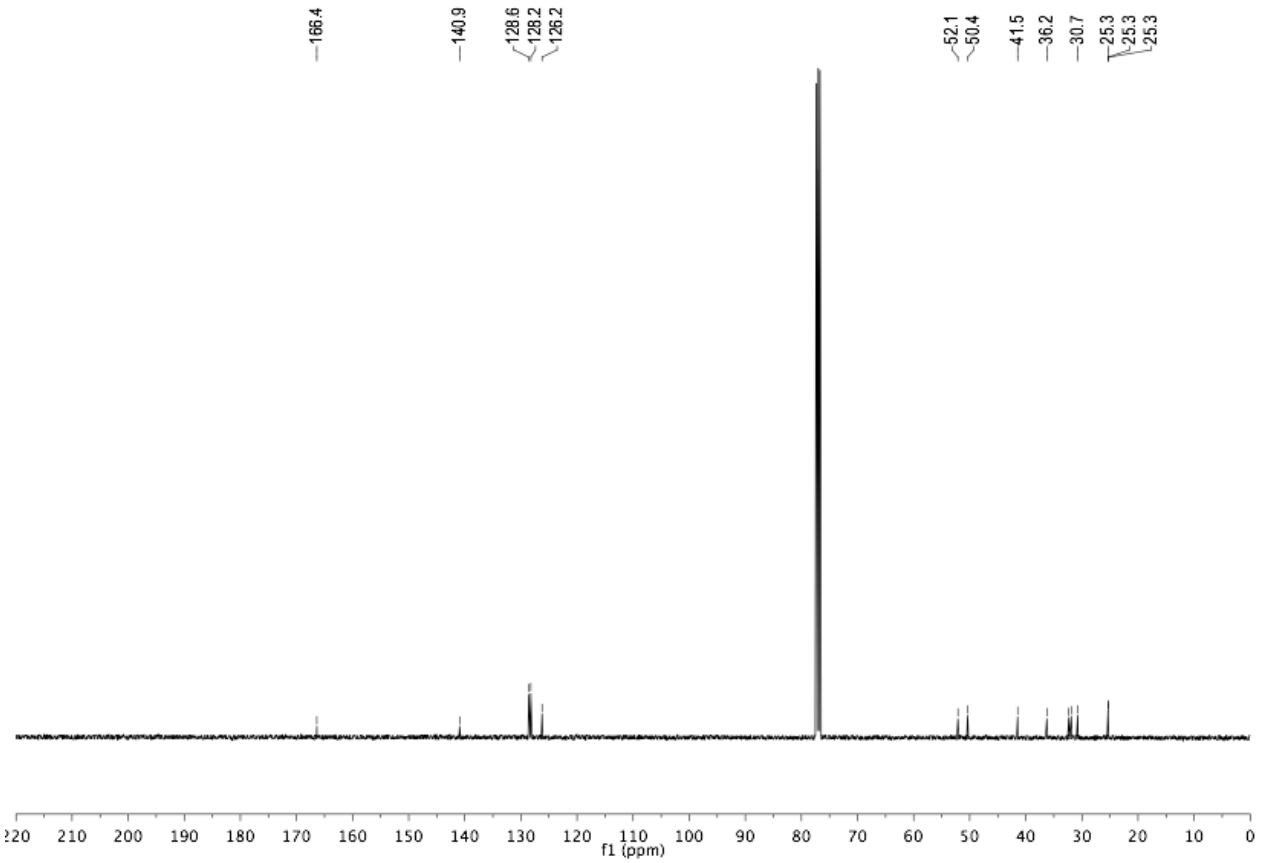


1-Cyclohexyl-4-phenethylazetidin-2-one (**218**)

^{1}H NMR ($CDCl_3$, 400 MHz)

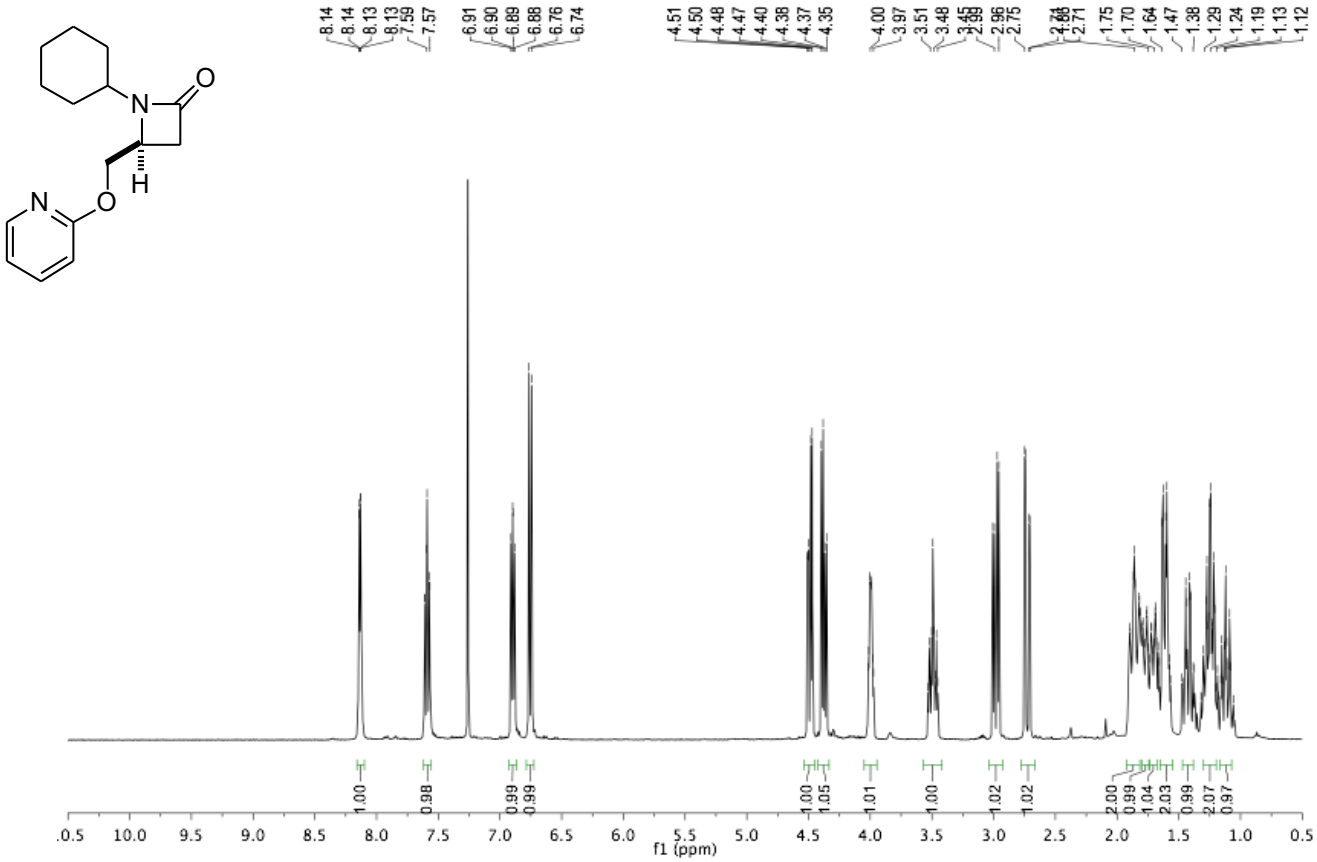


^{13}C NMR ($CDCl_3$, 100 MHz)

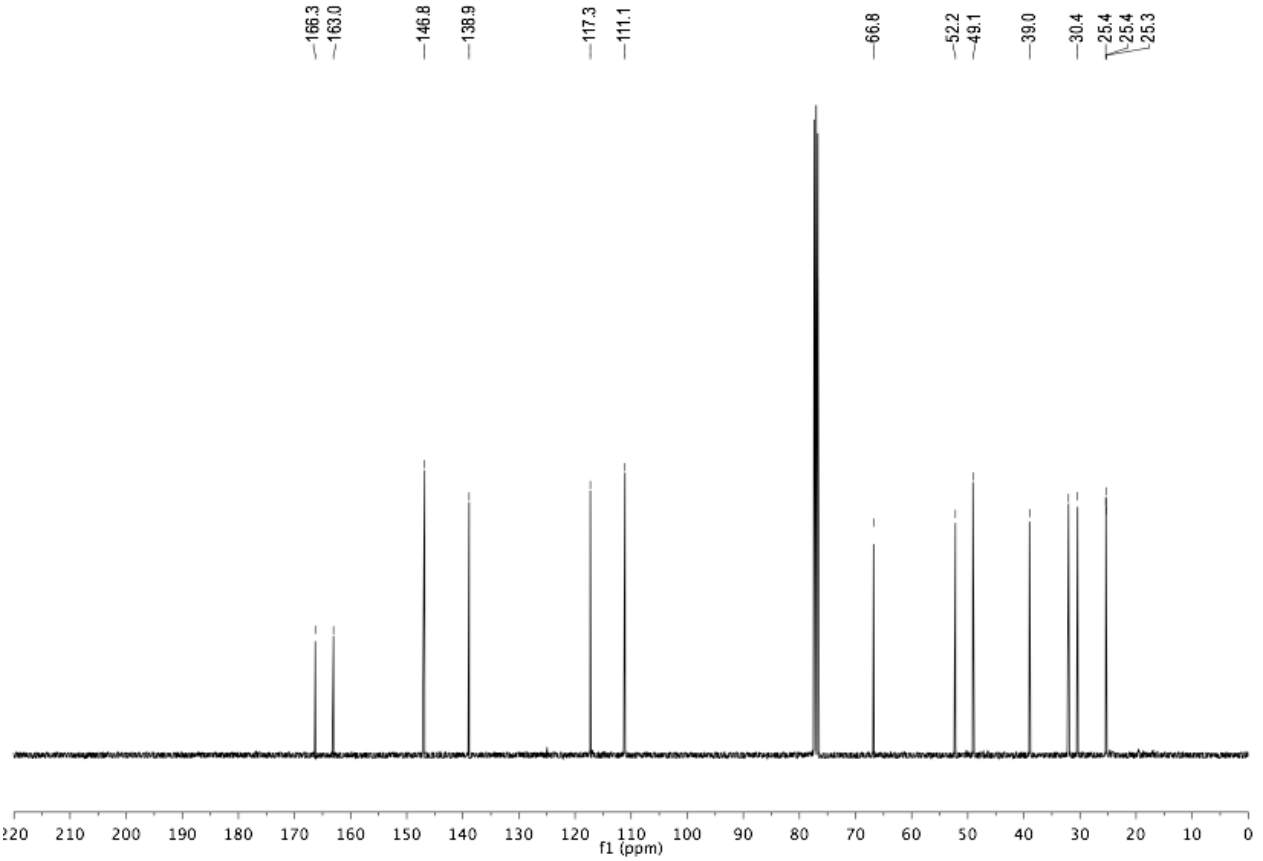


1-Cyclohexyl-4-((pyridin-2-yloxy)methyl)azetidin-2-one (**219**)

^{1}H NMR ($CDCl_3$, 400 MHz)

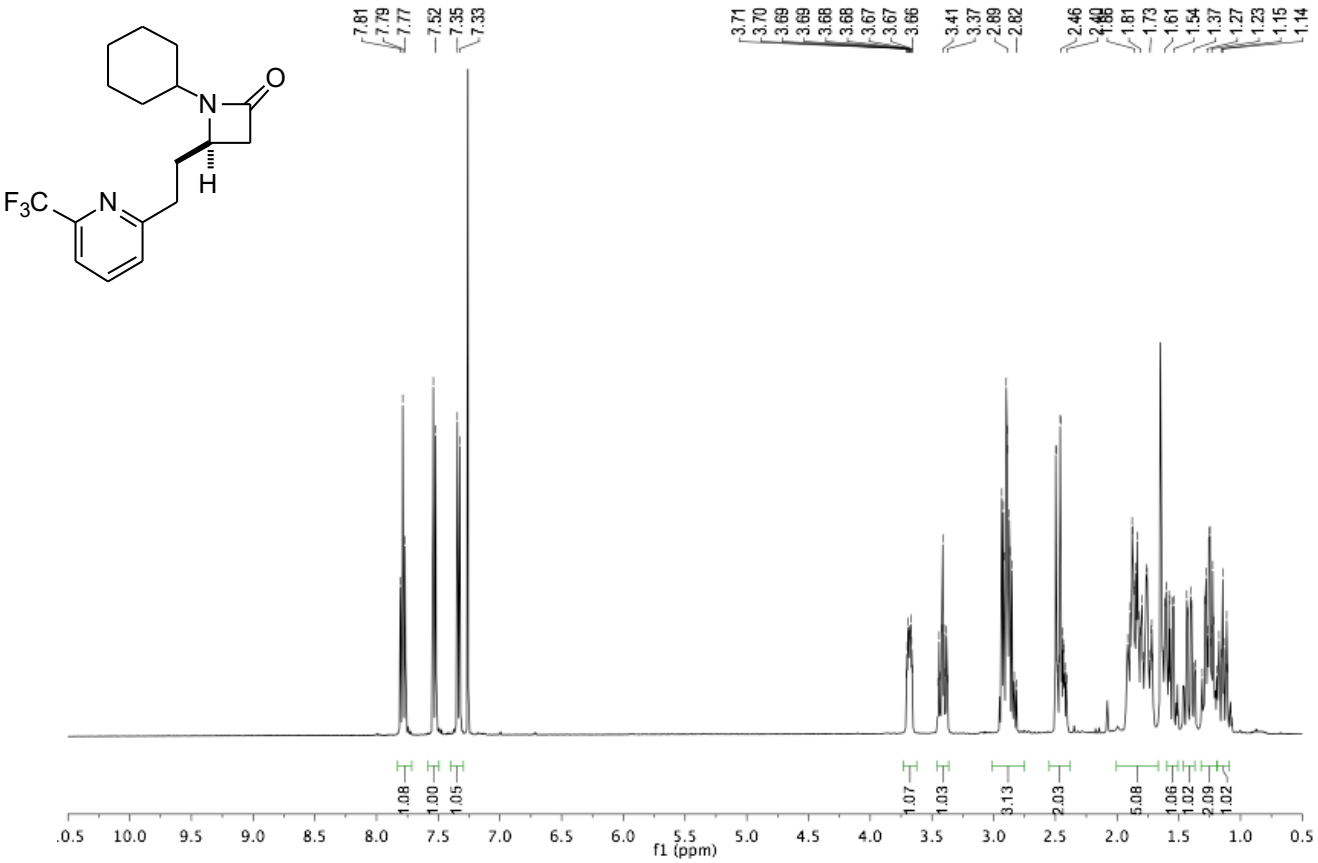


^{13}C NMR ($CDCl_3$, 100 MHz)

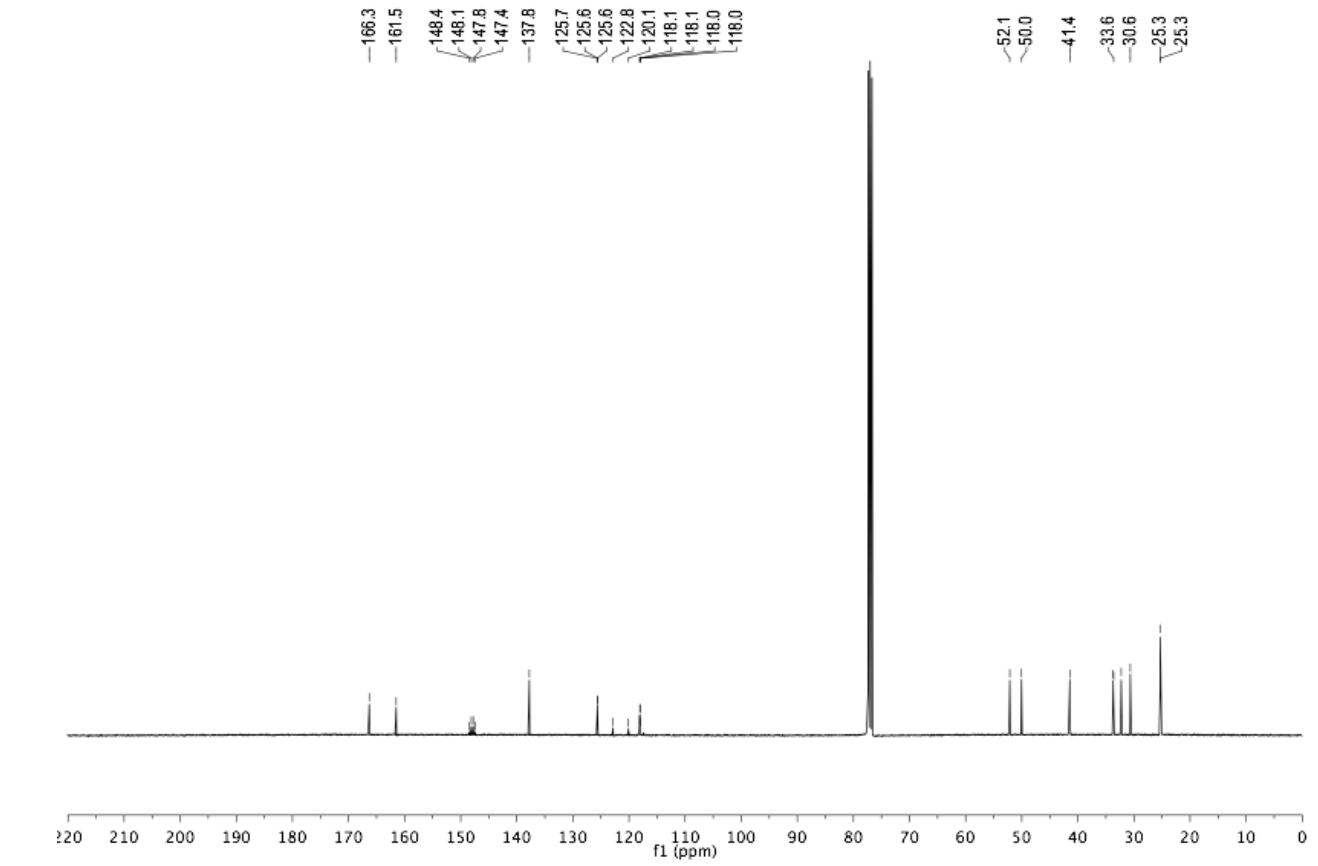


1-Cyclohexyl-4-(2-(6-(trifluoromethyl)pyridin-2-yl)ethyl)azetidin-2-one (**220**)

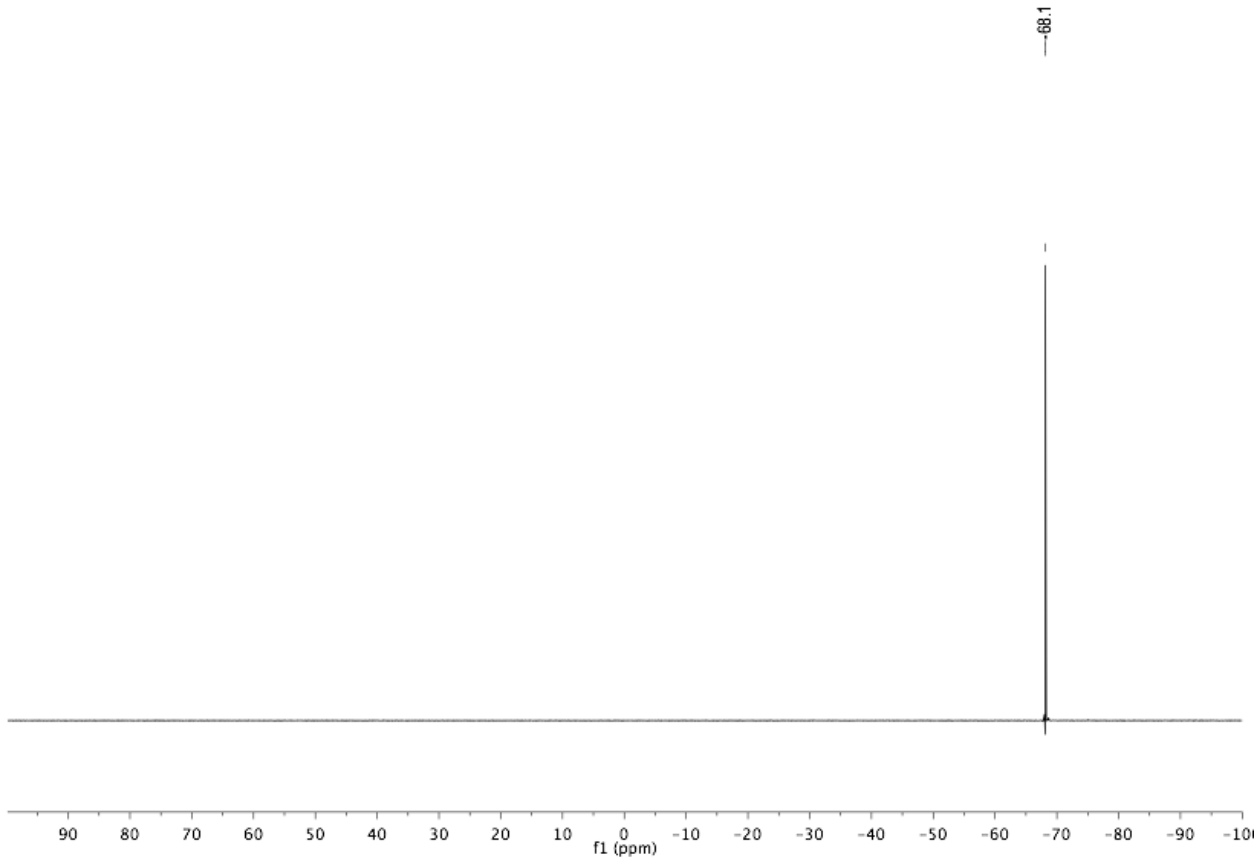
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)

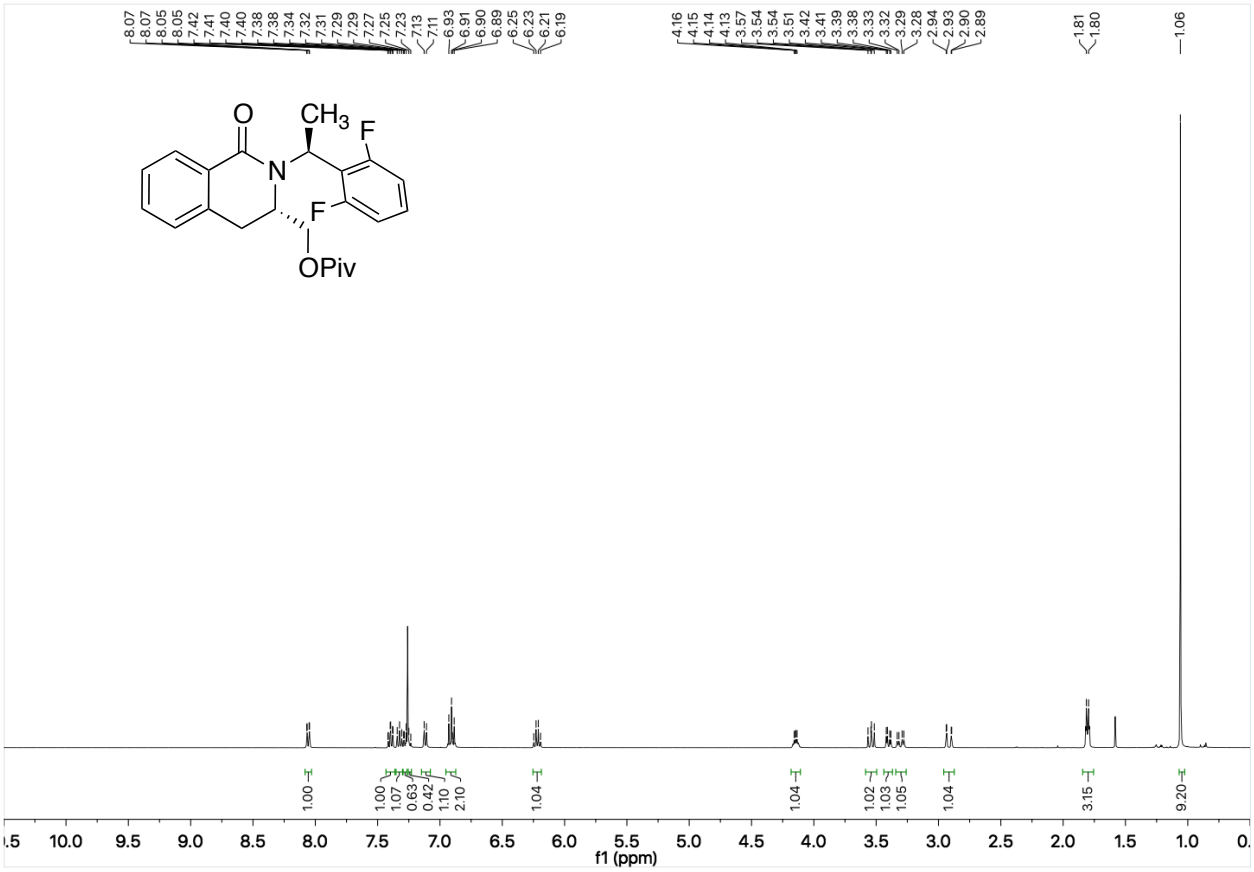


^{19}F NMR ($CDCl_3$, 376 MHz)

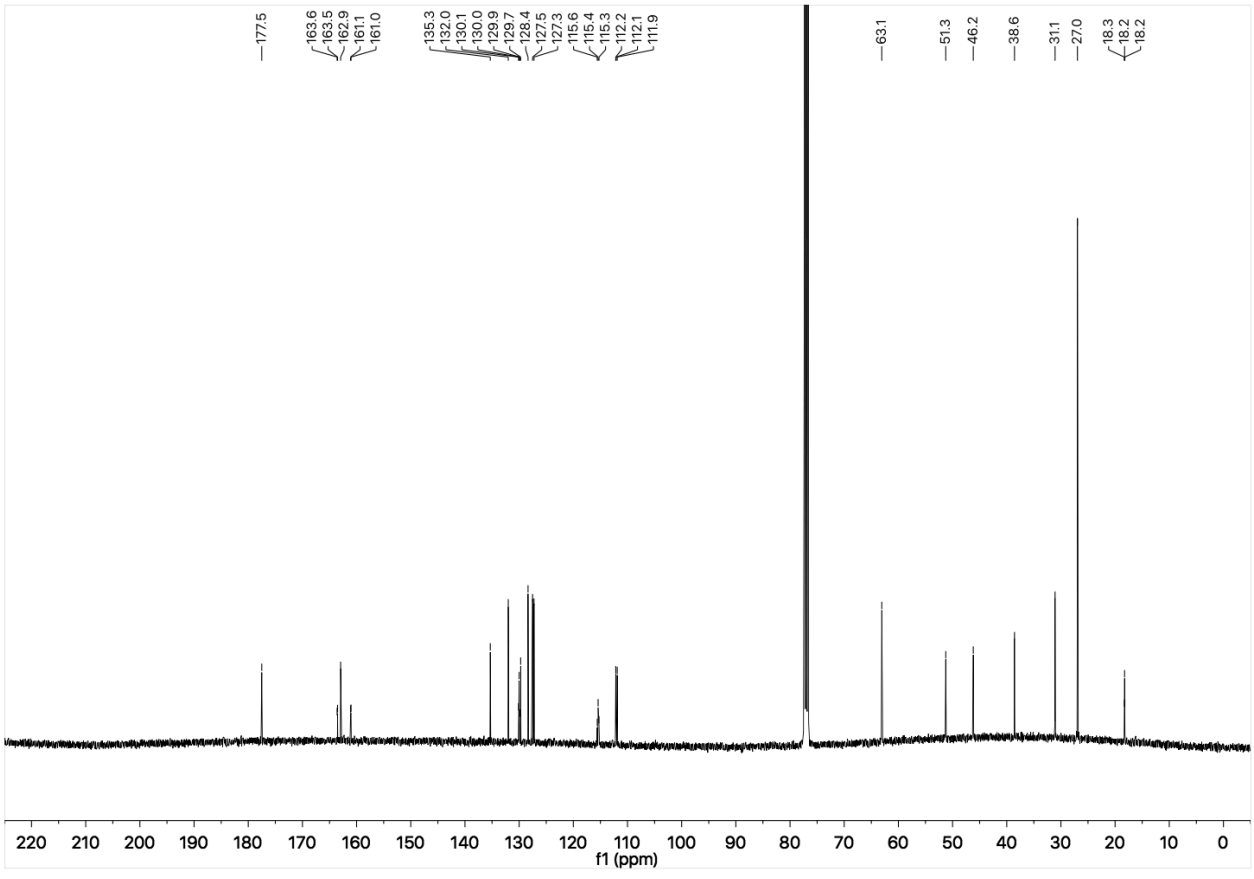


((S)-2-((S)-1-(2,6-difluorophenyl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl pivalate (**262**)

^{1}H NMR ($CDCl_3$, 400 MHz)



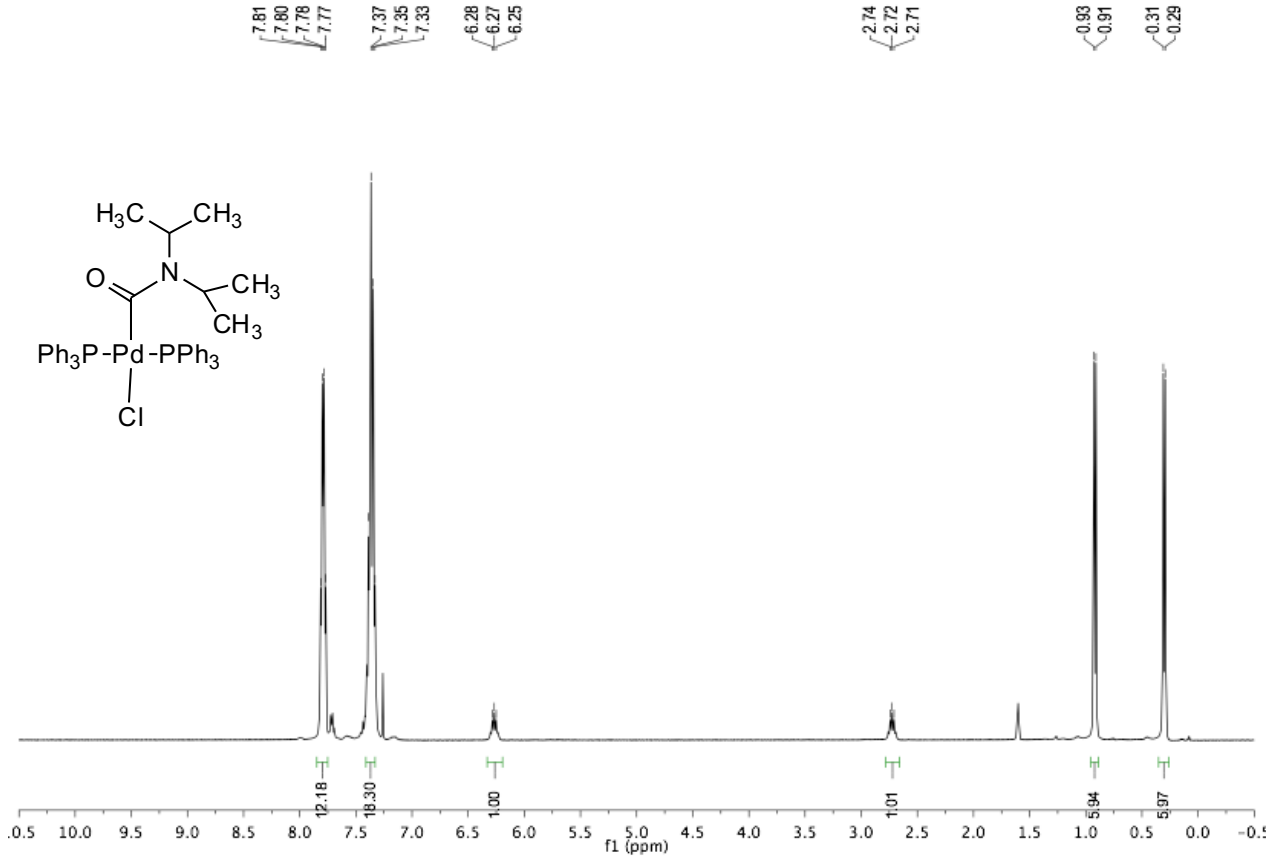
^{13}C NMR ($CDCl_3$, 100 MHz)



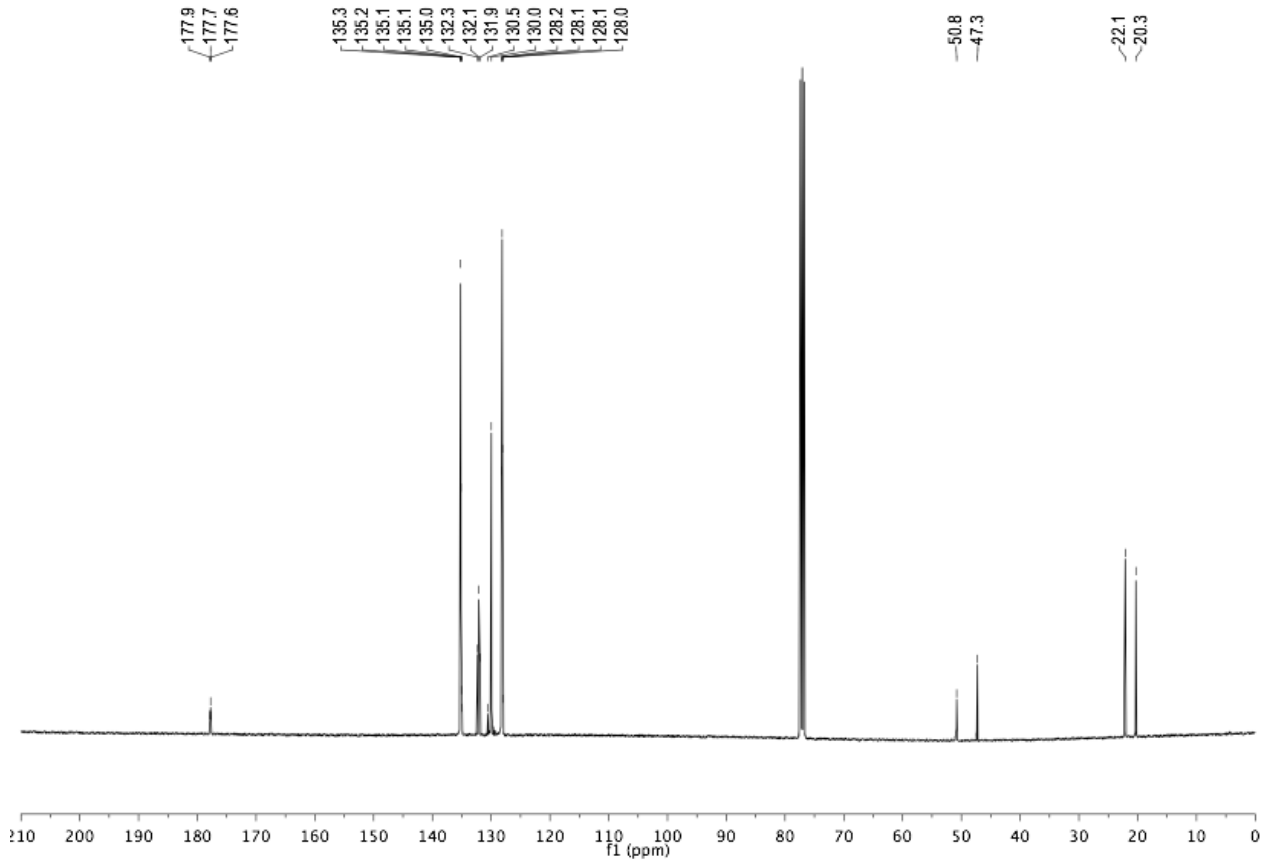
Palladium complexes

Bis(triphenylphospine) palladium diisopropyl carbamoyl chloride (**293**)

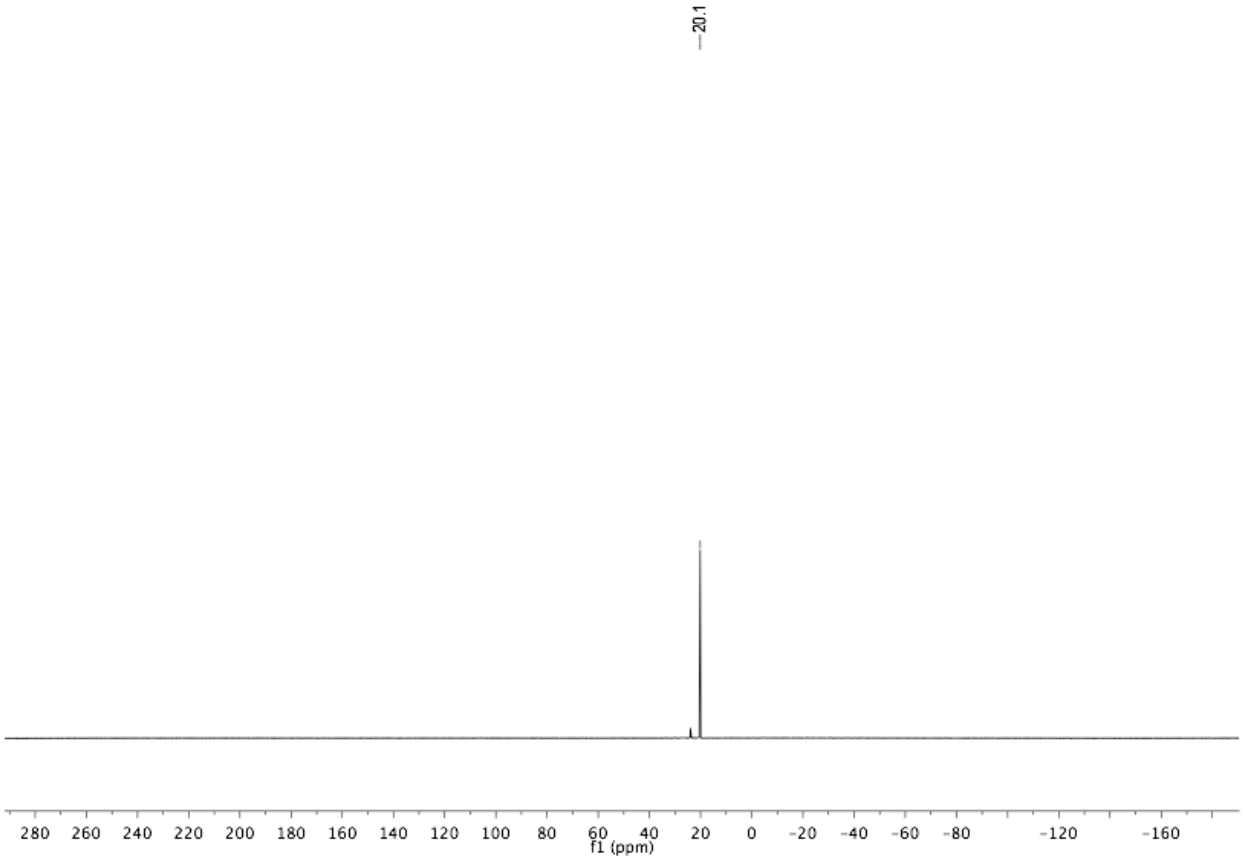
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)

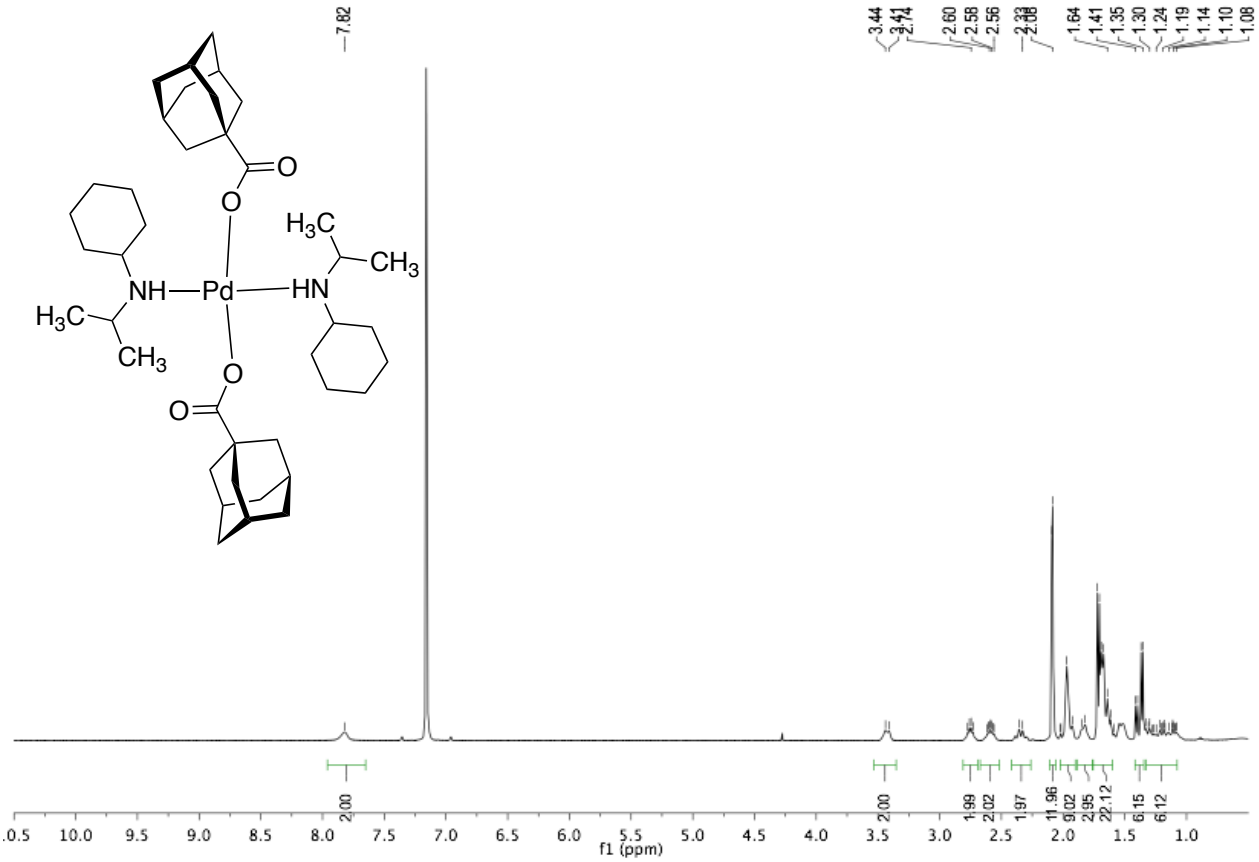


^{31}P NMR ($CDCl_3$, 162 MHz)

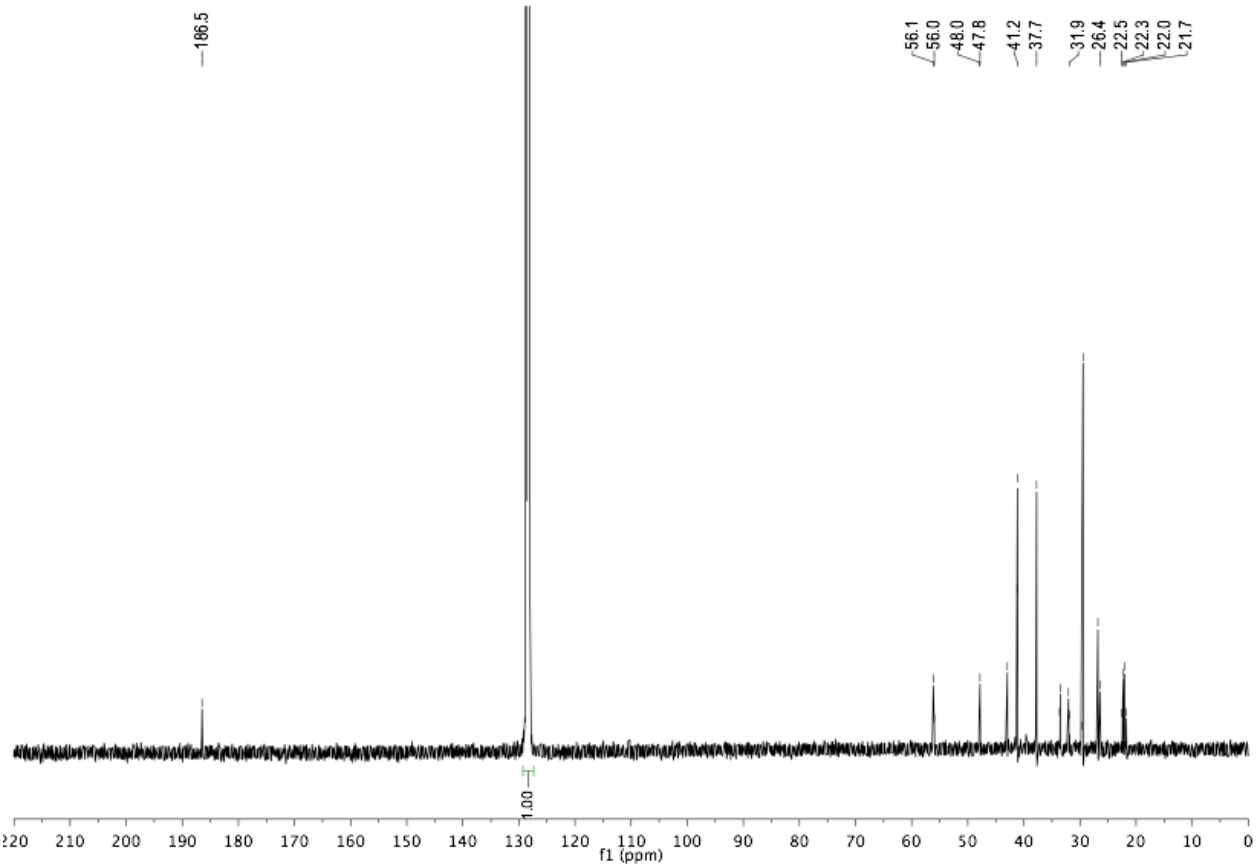


Bis(N-cyclohexylisopropylamine) palladium di-adamantoate (**274**)

^{1}H NMR (C_6D_6, 400 MHz)

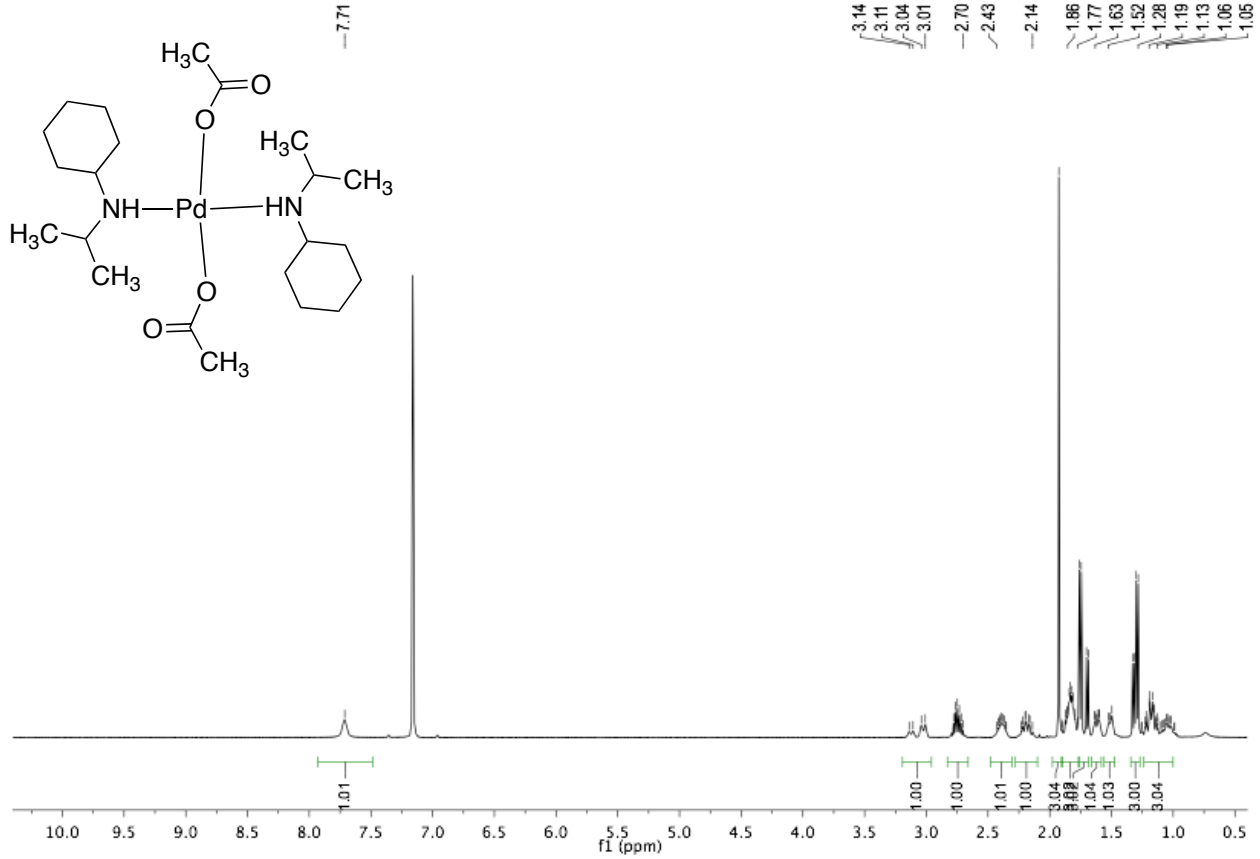


^{13}C NMR (C_6D_6, 100 MHz)

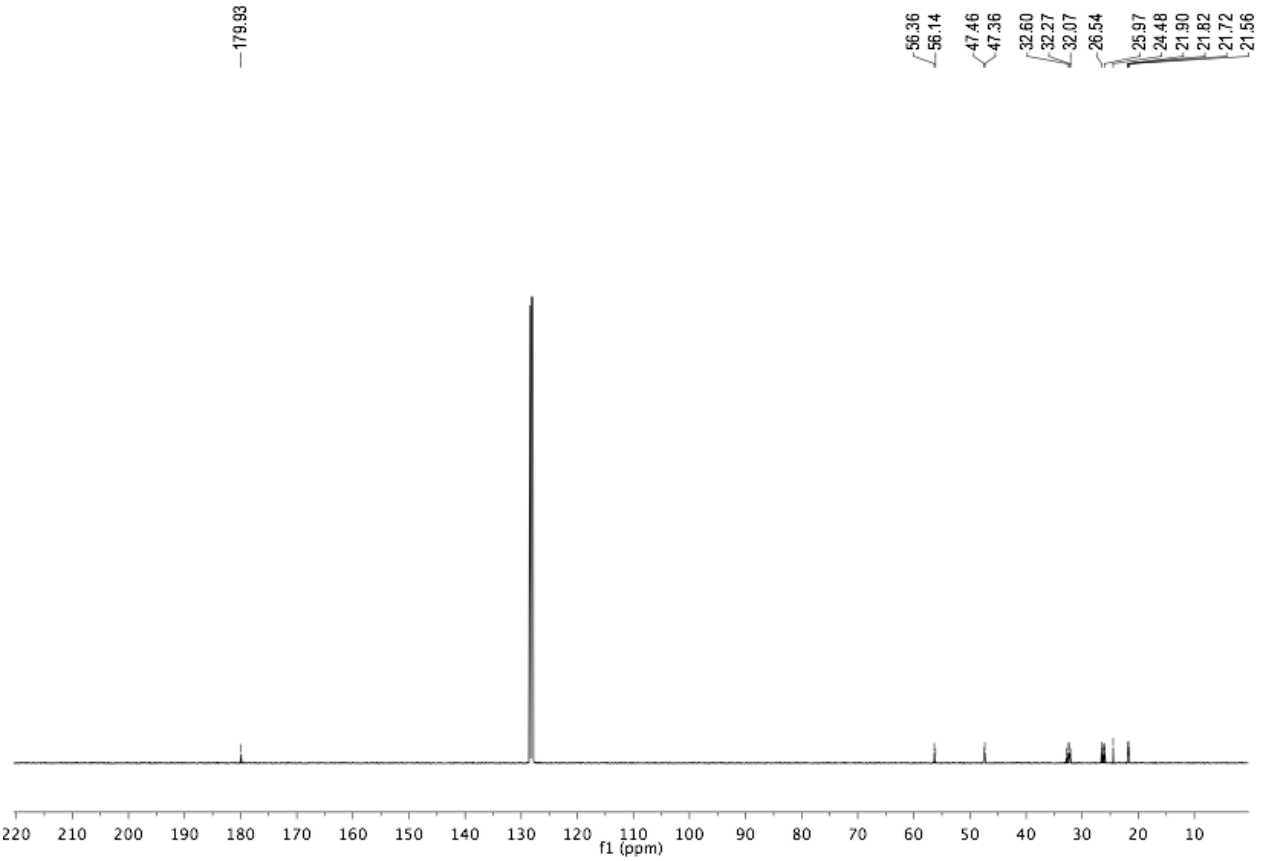


Bis(N-cyclohexylisopropylamine) palladium diacetate (**276**)

^{1}H NMR (C_6D_6, 400 MHz)

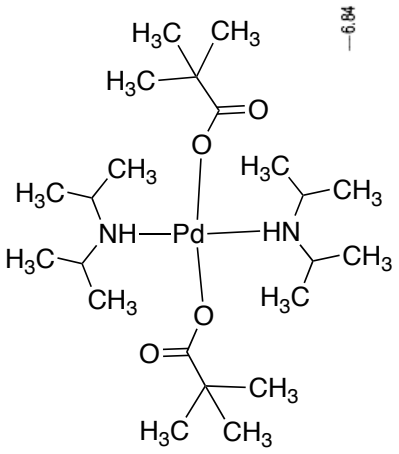


^{13}C NMR (C_6D_6, 100 MHz)

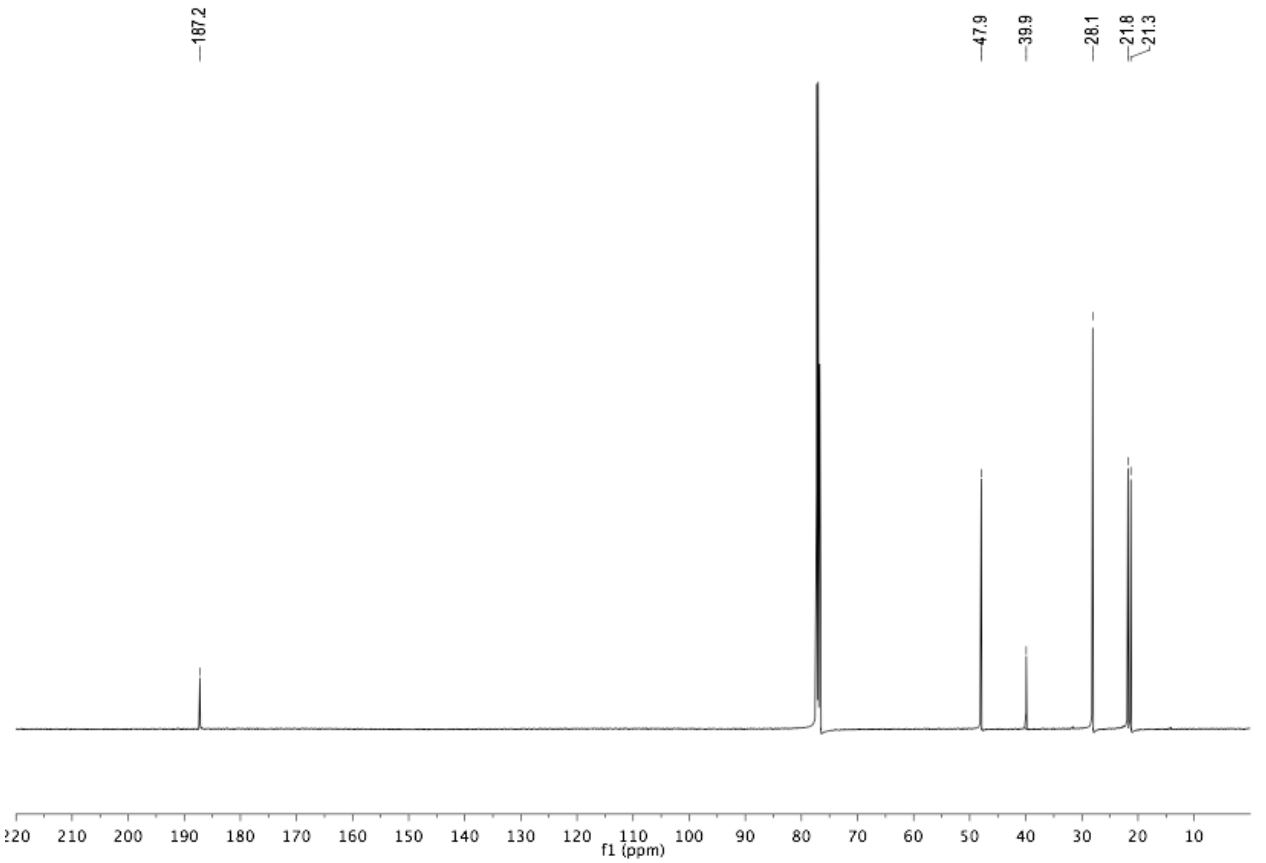


Bis(N-diisopropylamine)palladium dipivalate (**298**)

^{1}H NMR ($CDCl_3$, 400 MHz)

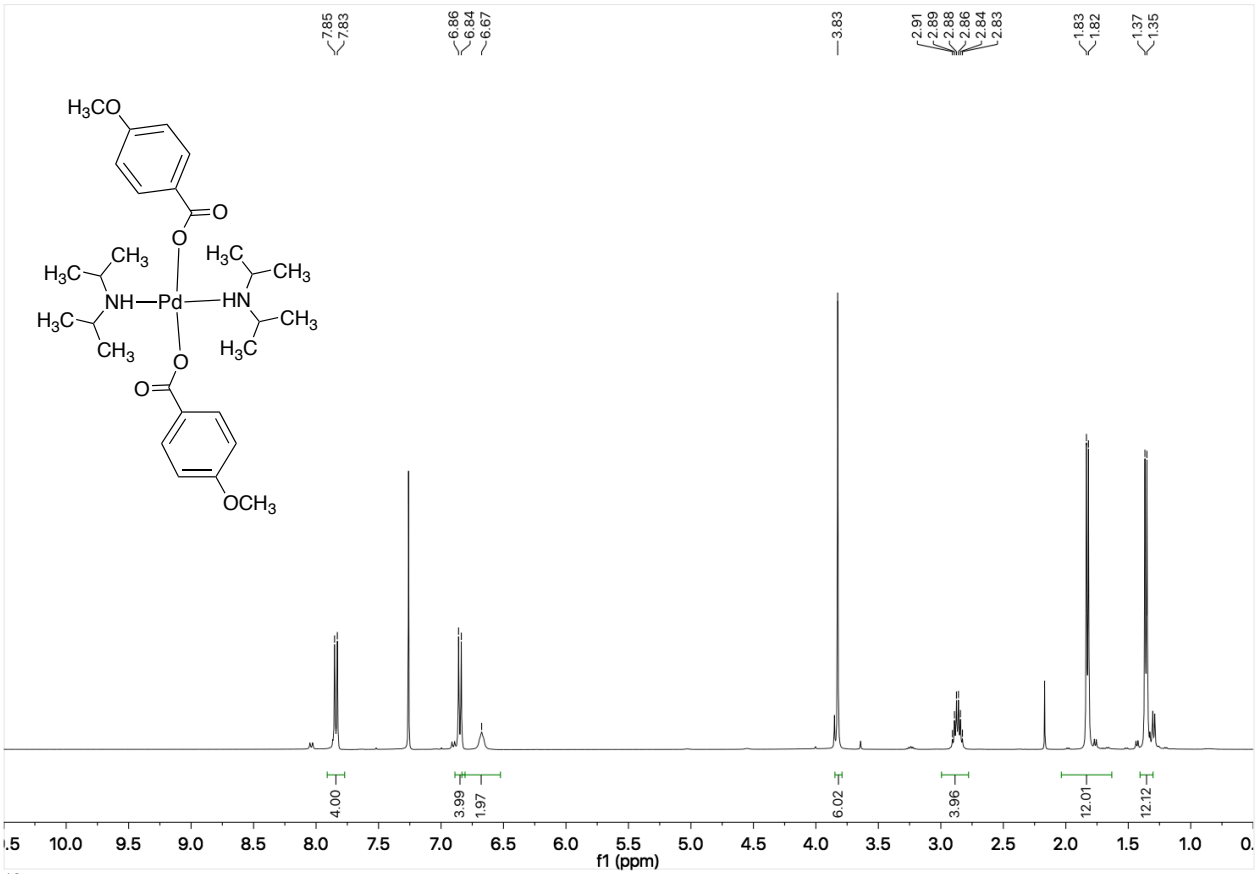


^{13}C NMR ($CDCl_3$, 100 MHz)

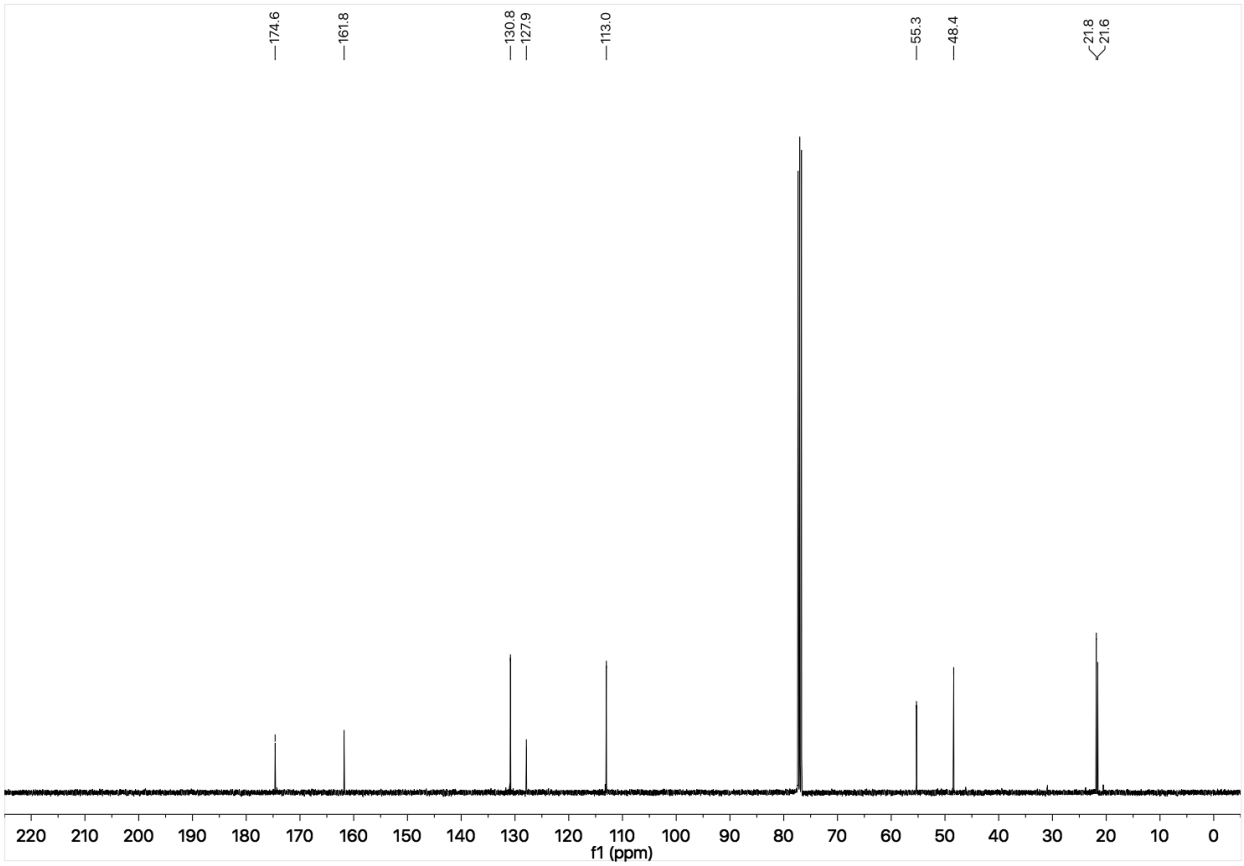


Bis(N-diisopropylamine) palladium diparamethoxybenzoate (**368**)

^{1}H NMR ($CDCl_3$, 400 MHz)

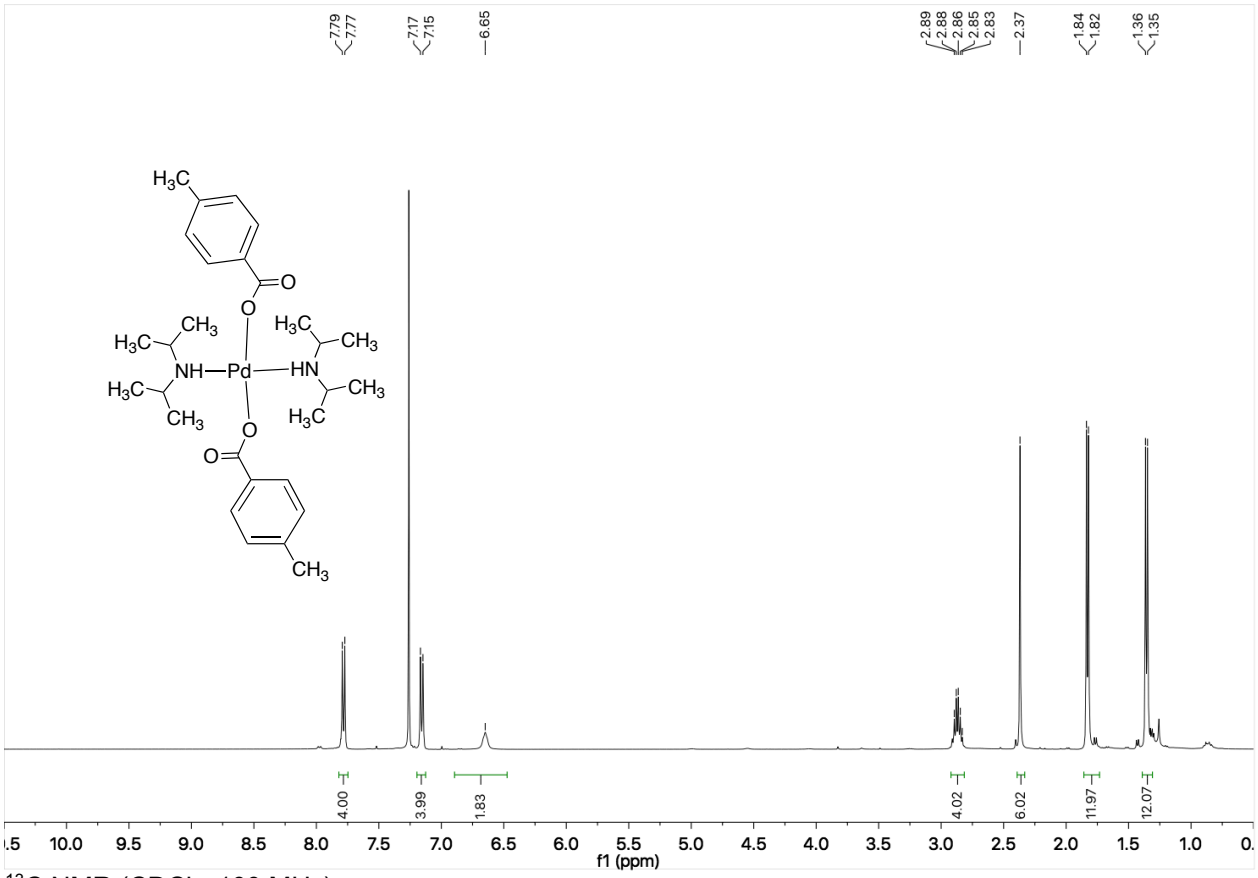


^{13}C NMR ($CDCl_3$, 100 MHz)

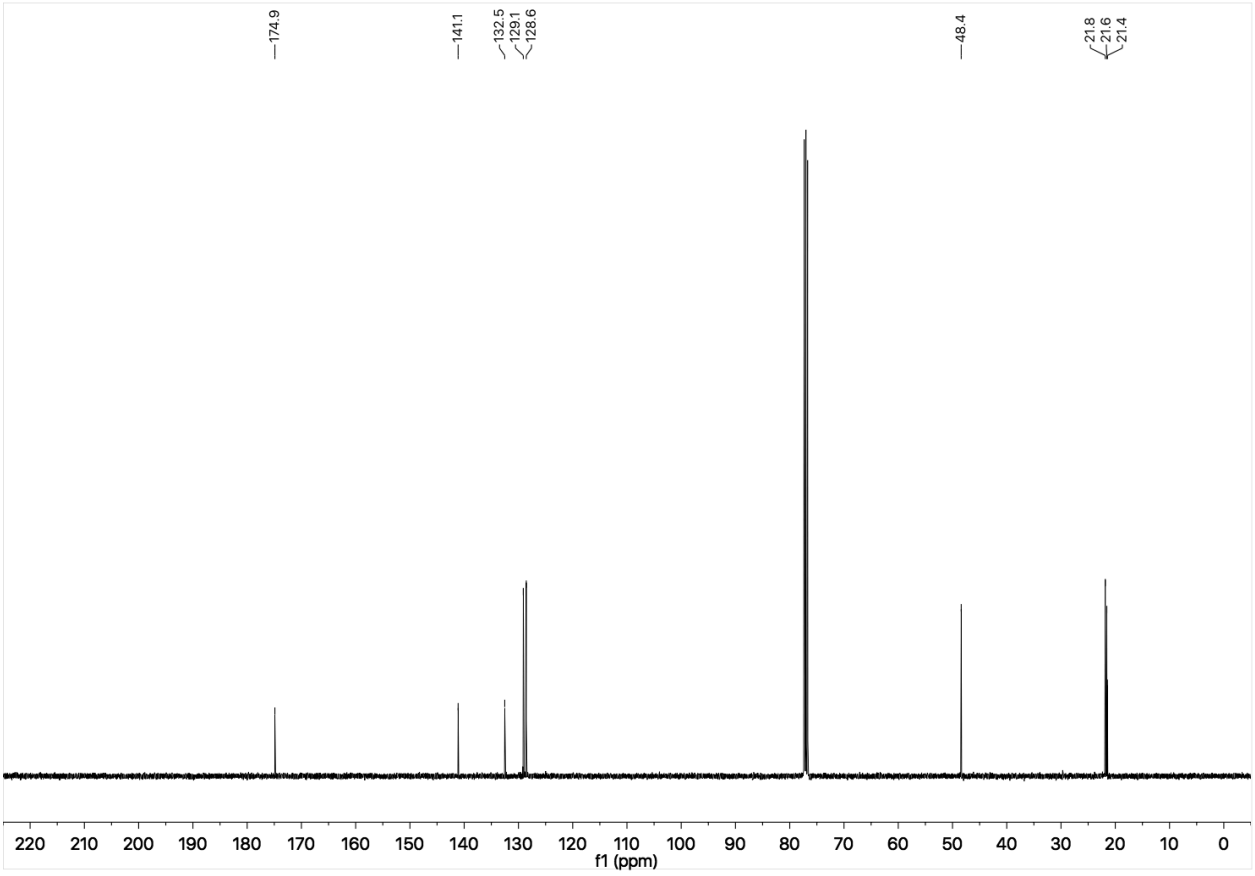


Bis(N-diisopropylamine) palladium diparamethylbenzoate (**369**)

^{1}H NMR ($CDCl_3$, 400 MHz)

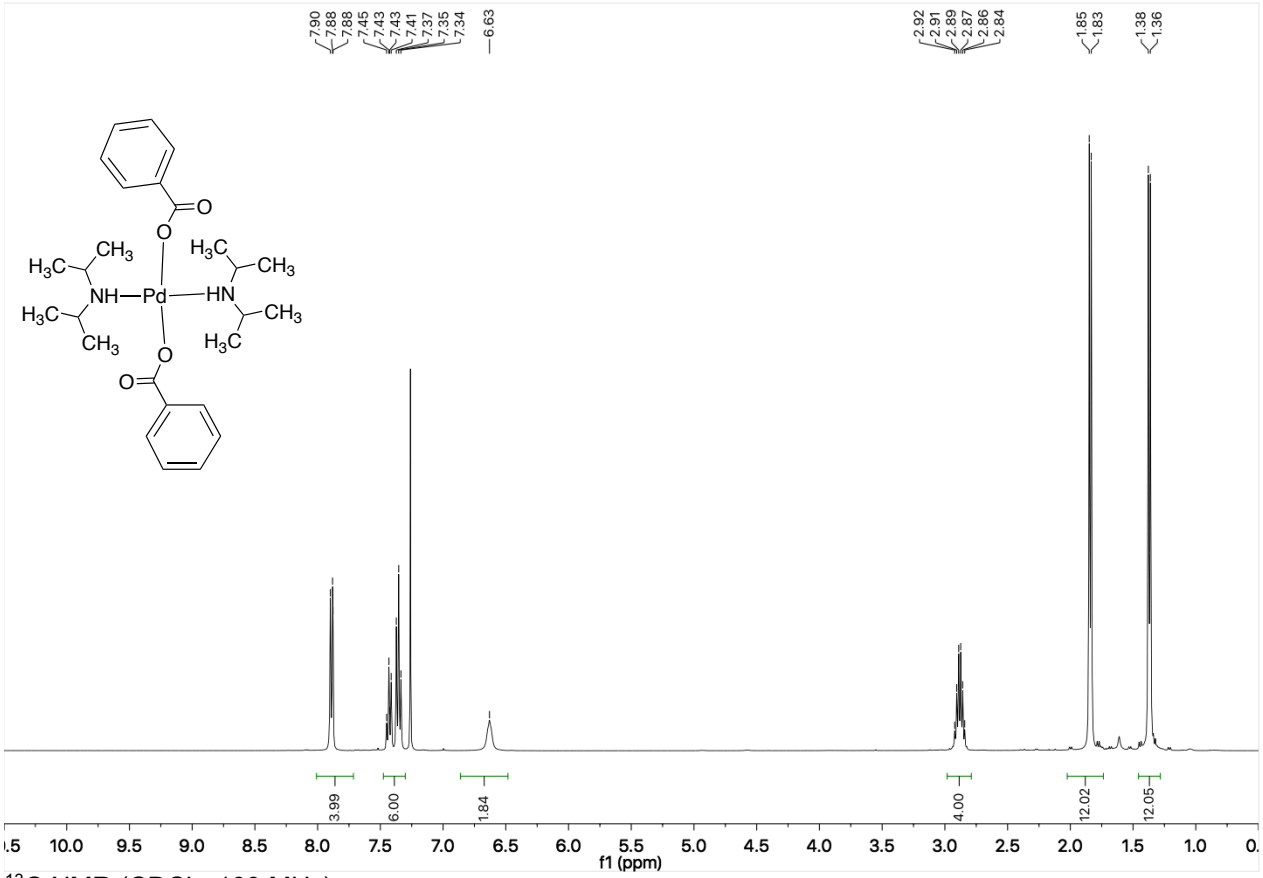


^{13}C NMR ($CDCl_3$, 100 MHz)

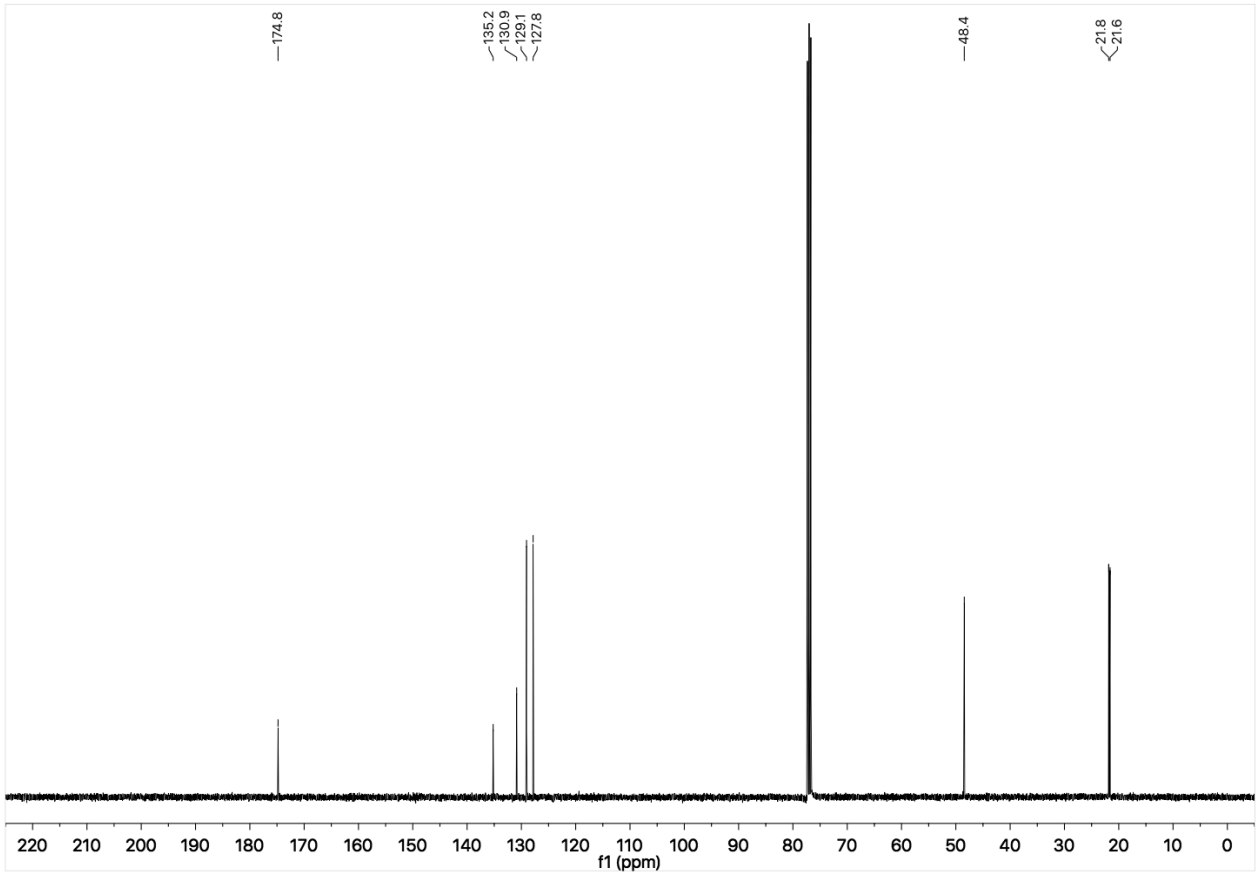


Bis(N-diisopropylamine) palladium dibenzoate (**370**)

^{1}H NMR ($CDCl_3$, 400 MHz)

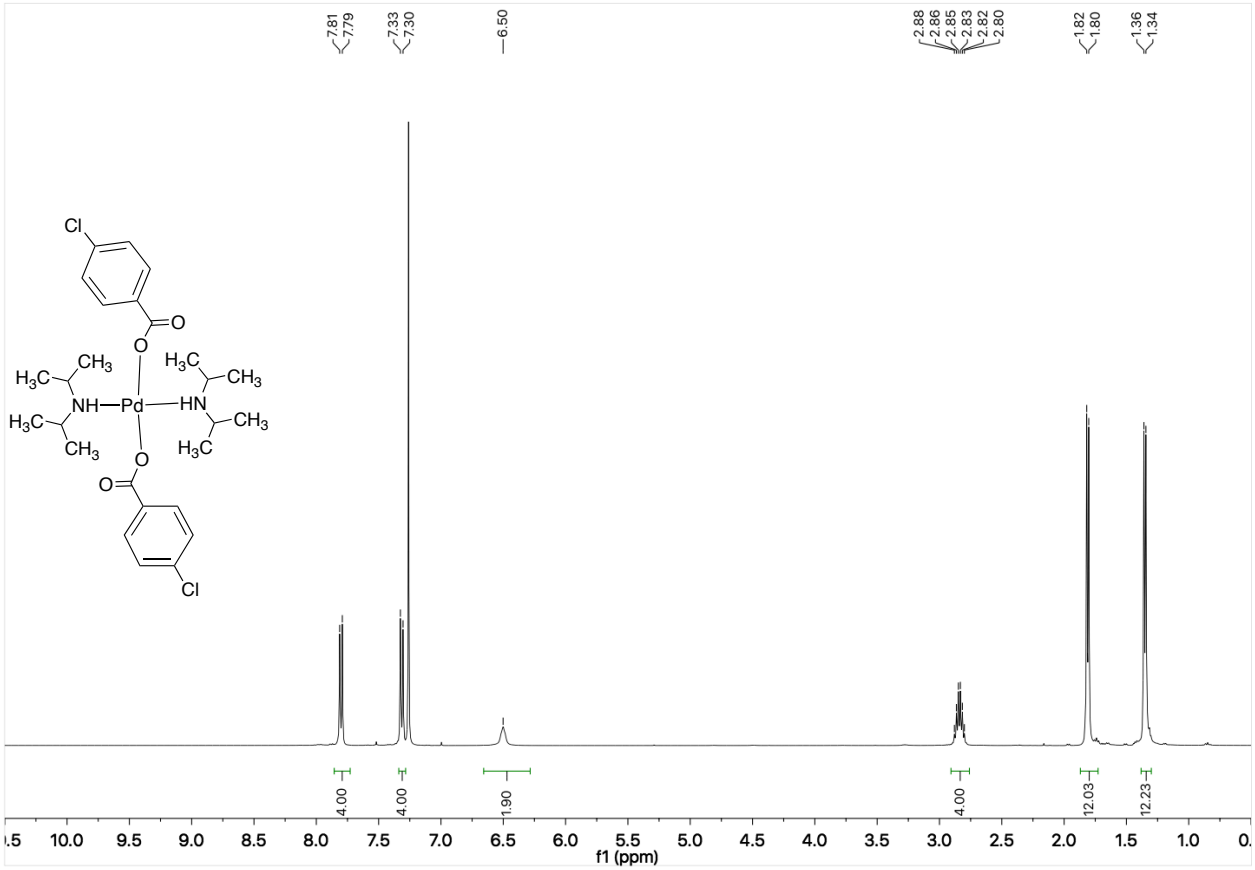


^{13}C NMR ($CDCl_3$, 100 MHz)

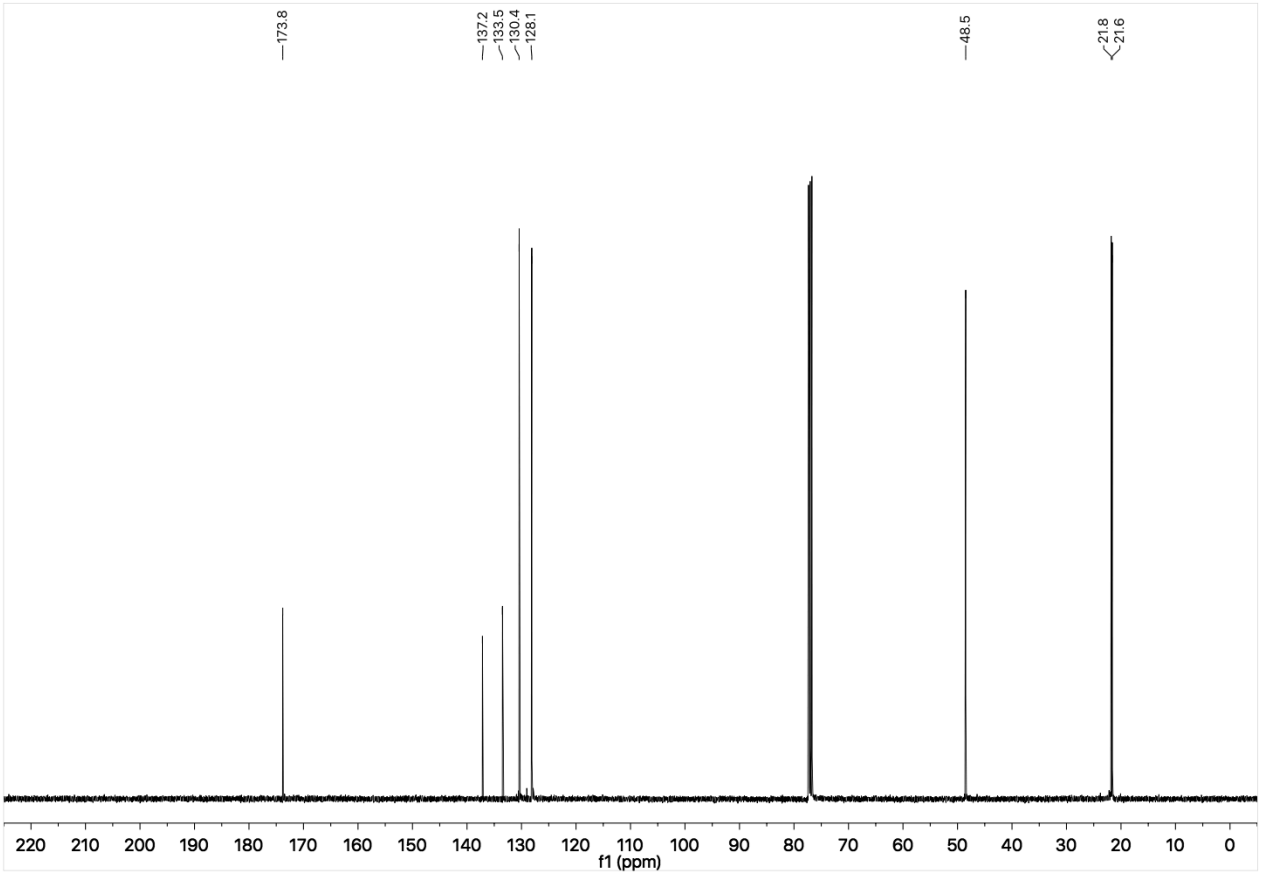


Bis(*N*-diisopropylamine) palladium diparachlorobenzoate (**371**)

^{1}H NMR ($CDCl_3$, 400 MHz)

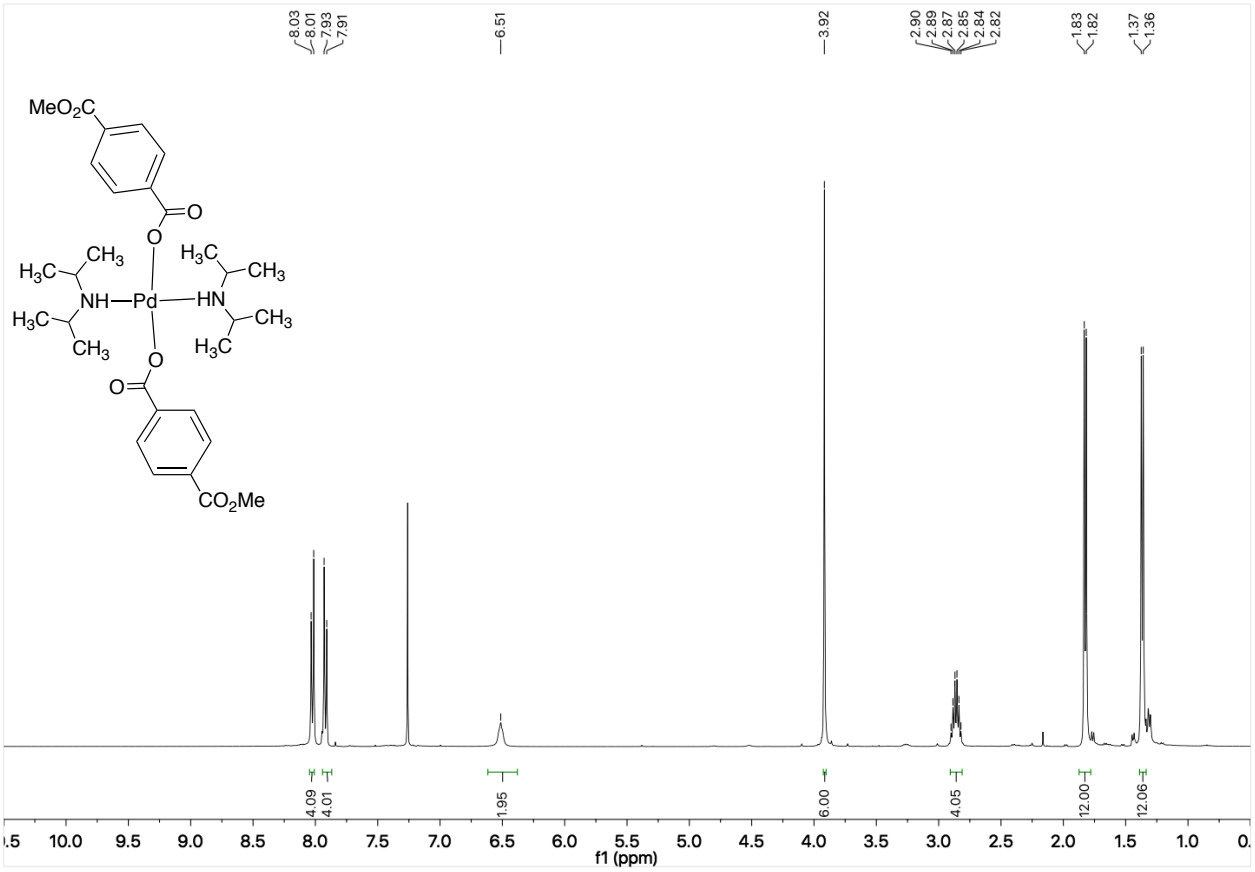


^{13}C NMR ($CDCl_3$, 100 MHz)

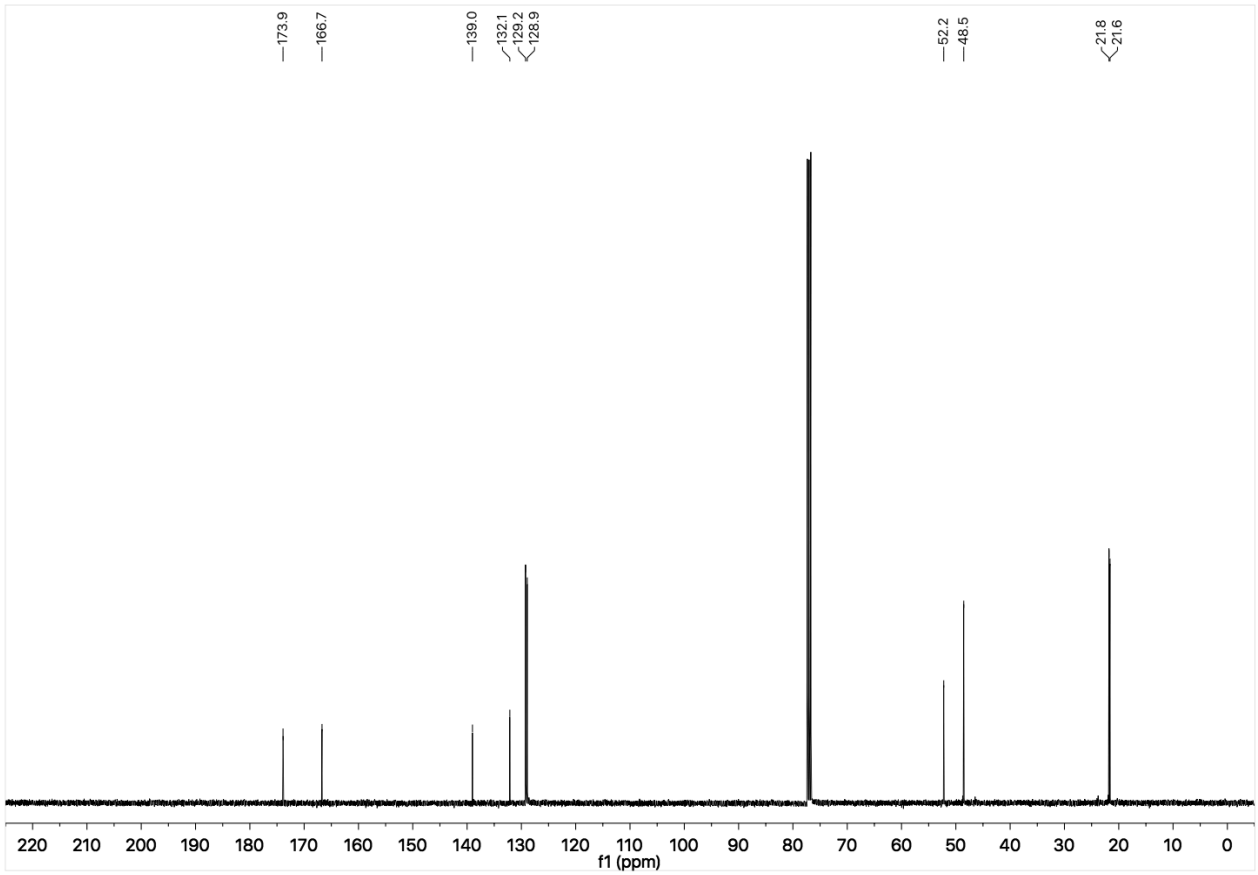


Bis(N-diisopropylamine) palladium diparamethoxycarbonylbenzoate (**372**)

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



Appendix 3: Published work

ORGANIC CHEMISTRY

A general catalytic β-C–H carbonylation of aliphatic amines to β-lactams

Darren Willcox,* Ben G. N. Chappell,* Kirsten F. Hogg, Jonas Calleja, Adam P. Smalley, Matthew J. Gaunt†

Methods for the synthesis and functionalization of amines are intrinsically important to a variety of chemical applications. We present a general carbon-hydrogen bond activation process that combines readily available aliphatic amines and the feedstock gas carbon monoxide to form synthetically versatile value-added amide products. The operationally straightforward palladium-catalyzed process exploits a distinct reaction pathway, wherein a sterically hindered carboxylate ligand orchestrates an amine attack on a palladium anhydride to transform aliphatic amines into β-lactams. The reaction is successful with a wide range of secondary amines and can be used as a late-stage functionalization tactic to deliver advanced, highly functionalized amine products of utility for pharmaceutical research and other areas.

The preparation and functionalization of amines is fundamental to a variety of chemical applications, such as the synthesis of medicinal agents, biologically active molecules, and functional materials (*1*). The best-established methods for amine synthesis involve carbon-nitrogen bond–forming processes based on alkylation (*2*), carbonyl reductive amination (*3*), and cross-coupling (*4*–*6*). Although recent advances in olefin hydroamination (*7*, *8*) and biocatalysis (*9*, *10*) have further expanded the toolbox of available transformations, the need for functional amines keeps the development of increasingly general catalytic reactions for amine synthesis at the forefront of synthetic organic chemistry. Inspired by the efficacy with which these well-established methods produce amines, we recognized the potential utility of a general catalytic process capable of directly introducing new functionality onto the framework of readily accessible and simple amines. In particular, we envisioned that their union with carbon monoxide through a selective amine-directed C–H carbonylation would produce a β-lactam feature, the versatile reactivity and biological relevance of which would make the method valuable to practitioners of synthetic and medicinal chemistry (Fig. 1A).

Transition metal catalysts capable of C–H activation have inspired intense research efforts within the synthetic chemistry community (*11*–*14*). Although many advances have been made in the field of aromatic sp^2-hybridized C–H [C(sp^2)–H] bond activation, functionalization of less reactive C(sp^3)–H bonds in aliphatic molecules continues to present a challenge (*15*). Because of the lower reactivity of C(sp^3)–H bonds, their activation often relies on the proximity to polar functional groups such as carboxylic acids (*16*, *17*), heteroarenes (*18*), and hydroxyl functionalities (*19*); aliphatic hydrocarbons containing the free-NH amino group, however, continue to cause problems that restrict wider application (*20*).

A number of factors can be identified that impede the development of free-NH aliphatic amine–directed C–H activation with catalysts such as Pd(II) salts (Fig. 1B): The high affinity of a free-NH amine for Pd(II) salts leads to the formation of stable bis(amine)-Pd complexes and can preclude catalysis; β-hydride elimination pathways often lead to oxidative degradation of the amine and catalyst reduction; and other polar functional groups can compete with the amine for coordination to the Pd catalyst, leading to poorly reactive or unselective systems. As a result, successful aliphatic amine–directed C–H activation typically requires the nucleophilicity of the nitrogen atom to be modulated by strongly electron-withdrawing protecting groups (*21*), directing auxiliaries (*22*–*25*), or an intensified steric environment around the NH motif (*26*, *27*). Despite the success of these methods, the additional functional and structural features that need to be incorporated into the amine framework for successful C–H activation can sometimes preclude downstream operations. Taken together, the limitations of current methods give weight to the appeal of a free-NH aliphatic amine–directed C–H activation process (Fig. 1A). Here we report the development of a general process for the catalytic C–H carbonylation of aliphatic amines, wherein readily available unprotected amines are combined with carbon monoxide to generate β-lactams. The design of a reaction pathway for C–H carbonylation controlled by a sterically hindered carboxylate ligand was crucial in overcoming the incompatibility of free-NH aliphatic amines and Pd(II) catalysts. There are a number of specific advantages of this method: First, readily available aliphatic amines can be directly converted into highly functionalized and synthetically versatile small-molecule lactam building blocks; second, by obviating the need for nitrogen-protecting or auxiliary groups, the number of synthetic steps required to access functional amines is greatly reduced; third, C–H carbonylation directed by free-NH amine motifs in pharmaceutical agents or natural products could be used as a potentially powerful late-stage functionalization approach to analog synthesis.

Carbon monoxide (CO) is an abundant chemical feedstock, and metal-catalyzed carbonylation reactions are integral to the laboratory- and manufacturing-scale synthesis of chemical products. Most of these processes involve CO binding to a metal to form a metal-carbonyl complex with well-established reactivity (*28*). Recently, our group described a sterically controlled C–H activation strategy for carbonylation of free-NH aliphatic amines (*26*). Highly hindered amines, displaying fully substituted carbon atoms on either side of the nitrogen motif, underwent C–H carbonylation to yield β-lactams (Fig. 2A). A key factor in the success of this strategy was the sterically induced destabilization of the readily formed bis(amine)-Pd(II) complex, resulting from a clash between the two highly hindered amines, which shifts the equilibrium toward a mono(amine)-Pd(II) species required for C–H activation. The anticipated pathway for these amine-directed reactions had been based on seminal studies by Fujiwara and colleagues (*29*), who outlined a mechanistic blueprint that has underpinned most subsequent directed C–H carbonylation reactions with Pd(II) catalysts: In our case, amine-directed cyclopalladation of the C–H bond formed a four-membered ring complex and was followed by coordination of CO, 1,1-migratory insertion to an acyl-Pd species, and reductive elimination to generate the carbonyl product. However, when the same reaction concept was applied to more commonly encountered, less hindered amines, the reaction failed or was low-yielding and resulted in oxidative degradation and acetylated amine products (Fig. 2A). Furthermore, we were not able to observe any trace of the corresponding four-membered-ring cyclopalladation complex, in contrast to the case for reactions with the hindered amine counterparts. Indeed, we calculated that a transition state for four-membered-ring cyclopalladation on these less hindered amines was too high to be a realistic pathway (*30*). On the basis of these observations, we reconsidered the classical mechanism for C–H carbonylation. CO is a strongly binding ligand, and it is perhaps surprising that it does not interact with the Pd catalyst before C–H activation. Moreover, $Pd(OAc)_2$ (Ac, acetate group) and CO display contrasting redox properties, and their combination predictably leads to catalyst reduction, which can complicate a catalytic process. Intrigued by the apparent paradox of the redox properties of the reagents, we became interested in the mechanism of CO-mediated reduction of $Pd(OAc)_2$, outlined in Fig. 2B. Although little is known about this pathway, studies by

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Moiseev and colleagues (*31*) provided clues that led us to propose a simplified model that we supported through computation. Two molecules of CO coordinate to monomeric $Pd(OAc)_2$ (**int-I**) and a calculated Pd–C–O angle of 153.7°, along with a bond distance between the carboxylate and CO of 2.06 Å, suggested an interaction between the two ligands. An attack on one of these CO ligands by a neighboring carboxylate was energetically favorable, leading to a Pd anhydride–type species, **int-II**. The transition state for this step (**int-I** to **int-II**) was calculated to be +11.50 kcal mol^{-1} relative to **int-I**. Coordination of a further CO (**int-III**) could trigger an intermolecular attack of the κ^1-bound acetate onto the distal carbonyl group of the anhydride, causing the release of CO_2, acetic anhydride, and Pd(0). Motivated by the potential reactivity of the putative Pd anhydride **int-II**, we postulated that attack by an amine on the proximal carbonyl would lead to a carbamoyl-Pd species (Fig. 2C), from which C–H activation would be possible. This unorthodox cyclopalladation pathway would lead to C–H activation two carbon atoms away from the nitrogen group—distinct from classical cyclopalladation processes that usually result in activation three carbons from the directing motif.

Reaction development and mechanistic studies

To test our hypothesis, we reacted amine **1a** under anticipated conditions for C–H carbonylation (Fig. 2D) (*32*, *33*). Although we observed the desired product (β-lactam **2a**) in low yield, the reaction was capricious and accompanied by the formation of acetylated amine and oxidative degradation products (entry 1). On the basis of our mechanistic blueprint, we expected that the attack on the Pd anhydride species at position **a** would lead to CO_2 release, reduction of the Pd catalyst, and an acetylated amine side product (Fig. 2B). We speculated that a larger carboxylate would generate a sterically biased Pd anhydride, steering the amine attack to position **b** to form the carbamoyl-Pd species and precluding the deleterious reduction pathway. Accordingly, addition of adamantanoic acid ($AdCO_2H$) to the standard reaction resulted in an increase in yield to 32% (entry 2). A similar improvement was observed when the original reaction was conducted in the presence of benzoquinone (BQ) (entry 3) (*34*). We found that the addition of both $AdCO_2H$ and BQ resulted in a dramatic increase in yield, with the β-lactam isolated in 65% yield (entry 4). The addition of nitrogen-containing ligands, such as quinoline **3a** or quinuclidine **3b**, enabled us to lower the amounts of the other reagents (entries 6, 7, and 9) (*35*). We also found that other hindered carboxylic acids were effective in the reaction (entry 8). An optimized procedure thus involved stirring a 0.1 M solution of amine **1a** in toluene with 10 mole (mol) % $Pd(OAc)_2$, 10 mol % $Cu(OAc)_2$, 100 mol % BQ, 25 mol % adamantanoic acid, and 10 mol % **3a** at 120°C under an atmosphere of CO; this gave an 83% yield of β-lactam **2a** after isolation. To probe the nature of the C–H activation step, we synthesized a derivative (**4**) of the proposed carbamoyl-Pd species (Fig. 2E). Under conditions that would create a similar chemical environment to the reaction (see Fig. 2D, entry 10, where PPh_3 is used as an additive), we showed that the β-lactam **2b** could be formed, albeit in low yield, supporting our hypothesis that C–H activation can occur through this carbamoyl-Pd intermediate (*36*).

A number of further preliminary mechanistic experiments were conducted to ascertain the role of the distinctive components of this C–H carbonylation process. First, we confirmed the importance of the sterically bulky carboxylate by comparing the reaction of the acetate- and adamantanoate-derived bis(amine)-Pd(II) carboxylate complexes (**5a** and **5b** in Fig. 3A) in the presence of BQ under a CO atmosphere; the yield of β-lactam from the acetate complex (**5a**) was 25%, compared with 89% from the adamantanoate complex (**5b**), supporting our hypothesis of a sterically controlled attack on the putative Pd anhydride species (Fig. 3A). Second, we identified BQ as essential for the high-yielding formation of **2a** from **5b:** In its absence, the yield drops from 89 to 26%, suggesting that BQ may play a mechanistic role in the pathway beyond that of an oxidant (*35*). Third, we deduced that although quinoline **3a** and quinuclidine **3b** additives increase the yield of β- lactam, they do not substantively affect the rate of the catalytic reaction. Last, we observed a kinetic isotope effect of 1.14 from parallel reaction of **1a** and ***d*^{6}-1a**, suggesting that C–H activation is not the rate-determining step (Fig. 3B). A close inspection of the reaction of ***d*^{6}-1a**, using nuclear magnetic resonance (NMR), revealed that hydrogen-deuterium scrambling had occurred in the lactam product **2a** at the

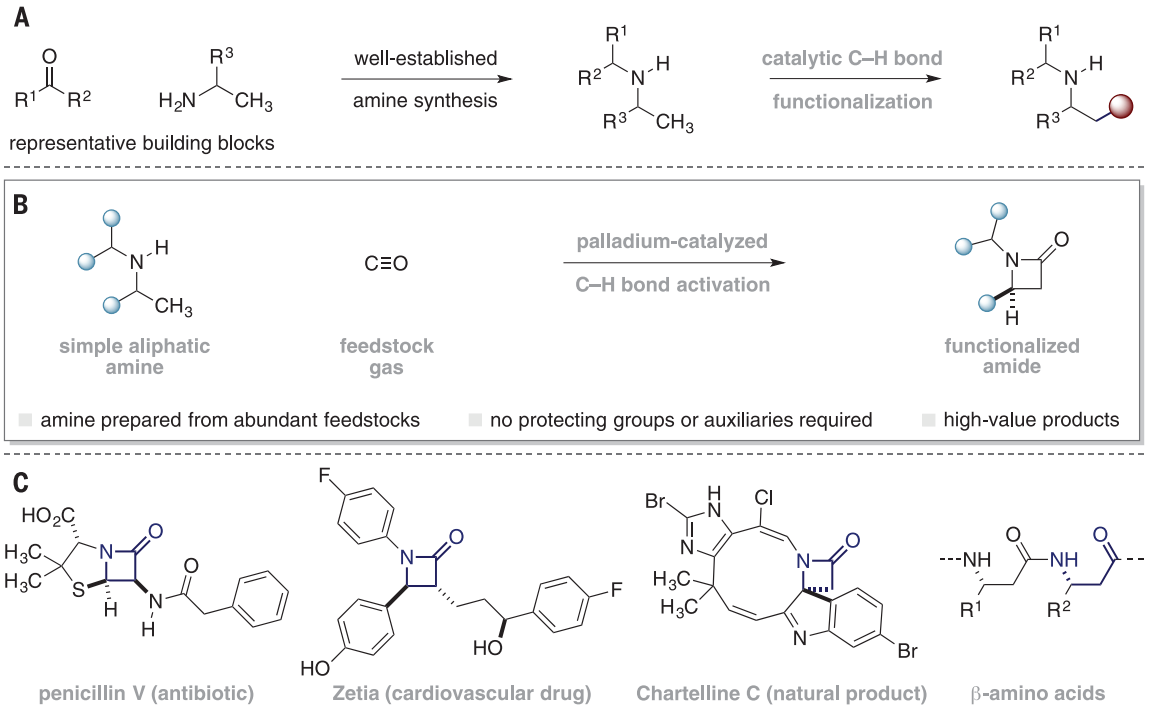


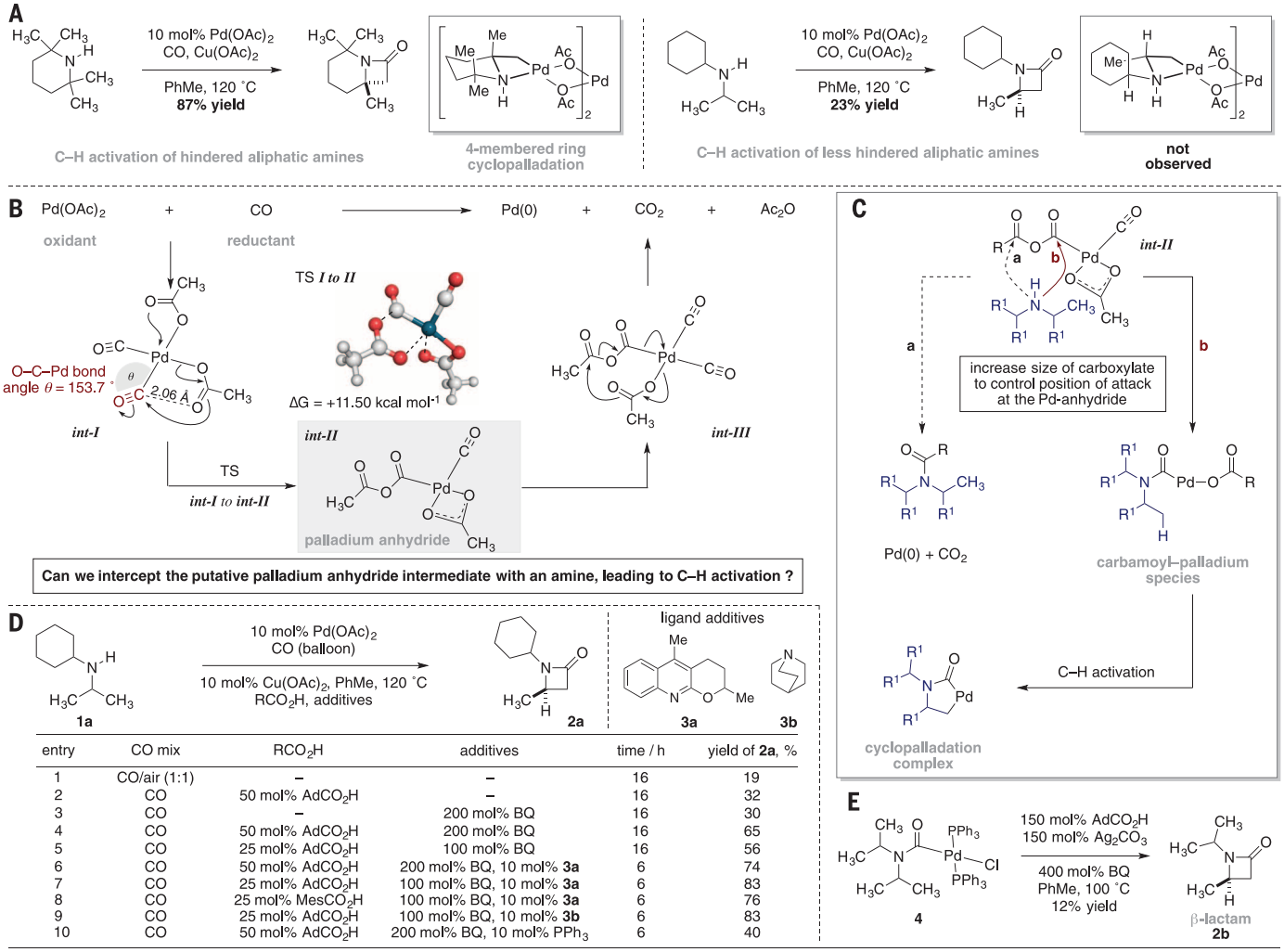
Fig. 1. A strategy for the catalytic synthesis of functionalized aliphatic amines. (**A**) Hypothesis: Combining well-established amine synthesis with metal-catalyzed C–H functionalization will lead to the rapid synthesis of functionalized amides. (**B**) Pd-catalyzed $C(sp^3)$–H carbonylation of free-NH amines. A blue circle or R denotes a general organic group. (**C**) The importance of β-lactams.

methyl group and at the position adjacent to the carbonyl of the amide. However, no hydrogen-deuterium scrambling was observed in the recovered starting material d^6-**1a**. These observations indicate that C–H activation is reversible and takes place after an irreversible step.

Taken together, these observations suggest a catalytic cycle for this C–H carbonylation reaction (*30*), which we have supported with a computational study of a simplified system using diisopropylamine **1b** and pivalic acid and without the involvement of **3a** or **3b** (Fig. 3C). The process begins with carboxylate exchange on $Pd(OAc)_2$: Coordination of the sterically hindered acid (RCO_2H) (R, *t*-butyl group) forms $Pd(O_2CR)_2$ or a mixed carboxylate complex. Next, amine coordination forms the mono(amine)-Pd(II) complex **int-IV**, which is in equilibrium with the off-cycle bis(amine)-Pd(II) complex (**int-V**); we deemed **int-V**, as the catalyst resting state, to be the energetic reference point. CO binding then forms **int-VI**, from which a viable transition state (**TS1**) to the Pd anhydride complex **int-VII** was determined. On the basis of our kinetic isotope effect and computational studies, we suggest that the attack of the amine at the internal carbonyl of **int-VII** (via **TS2**) to form carbamoyl-Pd species **int-VIII** is irreversible, and from this point, reversible C–H activation takes place through a concerted metalation deprotonation pathway (**TS3**) to form a five-membered-ring cyclopalladation intermediate **int-IX** (see also Fig. 2E). Last, BQ-assisted reductive elimination (via **TS4**) leads to β-lactam **2b** after decomplexation from Pd(0); oxidation of the Pd(0) species with $Cu(OAc)_2$ regenerates the active Pd(II) species. The amine additives **3a** and **3b** may stabilize the Pd(0) species before oxidation by preventing deactivating aggregation (*37*). This effect may be more pronounced toward the end of the reaction, when the concentration of the amine substrate **1** is lower, and possibly explains why **3a** and **3b** have an effect on yield but not on the rate of reaction.

Substrate scope with simple amines

Having established optimal reaction conditions and validated a possible reaction mechanism, we focused our efforts on establishing the scope of the C–H carbonylation process. In setting a benchmark, we targeted a substrate scope that would encompass all structural classes of aliphatic secondary amines with respect to substitution at the carbon atoms directly connected to the free-NH group. We previously reported a C–H activation strategy for fully substituted aliphatic secondary amines that proceeds via four-membered-ring cyclopalladation—a pathway distinct from



entry	CO mix	RCO_2H	additives	time / h	yield of **2a**, %
1	CO/air (1:1)	–	–	16	19
2	CO	50 mol% $AdCO_2H$	–	16	32
3	CO	–	200 mol% BQ	16	30
4	CO	50 mol% $AdCO_2H$	200 mol% BQ	16	65
5	CO	25 mol% $AdCO_2H$	100 mol% BQ	16	56
6	CO	50 mol% $AdCO_2H$	200 mol% BQ, 10 mol% **3a**	6	74
7	CO	25 mol% $AdCO_2H$	100 mol% BQ, 10 mol% **3a**	6	83
8	CO	25 mol% $MesCO_2H$	100 mol% BQ, 10 mol% **3a**	6	76
9	CO	25 mol% $AdCO_2H$	100 mol% BQ, 10 mol% **3b**	6	83
10	CO	50 mol% $AdCO_2H$	200 mol% BQ, 10 mol% PPh_3	6	40

Fig. 2. Toward an activation mode for C–H carbonylation of unhindered aliphatic amines. (**A**) Previous work: C–H carbonylation of hindered aliphatic amines via a four-membered-ring cyclopalladation pathway (left) and poor-yielding C–H carbonylation of less hindered amines (right). (**B**) Reduction of $Pd(OAc)_2$ by CO. (**C**) Design: A sterically controlled ligand-enabled C–H activation. (**D**) Optimization studies. (**E**) C–H activation from a de novo carbamoyl-Pd complex. Computational studies were conducted using Amsterdam Density Functional software at the ZORA:BLYP-D3/TZ2P level with the COSMO solvation model (PhMe) (supplementary materials). Ph, phenyl group; Me, methyl group; Ac, acetate group; BQ, benzoquinone; Ad, adamantyl group; $MesCO_2H$, 2,4,6-trimethylbenzoic acid; Δ*G*, change in Gibbs free energy; TS, transition state; int, intermediate; h, hours; equiv, equivalent.

this process (*26*). However, the majority of amines in everyday use are represented by less substituted variants. Each class of these amine starting materials can be prepared by classical methods of C–N bond formation, thereby linking the C–H activation process to well-established preparative methods and reliable chemical feedstocks. Figure 4 shows the wide breadth of the substrate scope for this aliphatic amine C–H activation process. We began by assessing amines with five substituents around the nitrogen motif and found that these hindered secondary amines were compatible with the reaction conditions and could be efficiently converted into the corresponding β-lactams in good yields (**2c** to **2i**). In the case of **2d**, classical amine-directed five-membered-ring cyclopalladation could potentially lead to a γ-lactam product; however, only the product formed via the new carbonylation pathway was observed. Amines with an unsymmetrical arrangement of four substituents around the NH motif also worked very well in the C–H activation process (**2j** to **2s**). A variety of useful functional groups were amenable to the reaction conditions, producing the β-lactam products in good yields. The reaction with amines containing two substituents on either side of the free-NH amine motif (**2a**, **2b,** and **2t** to **2af**) tolerated the incorporation of protected hydroxyl motifs (**2u** and **2af**), carbonyls (**2w**), and amine motifs (**2ab**, **2ad**, and **2ae**) into the β-lactam products, providing opportunities for downstream synthetic manipulations of these valuable products. Pyridines (**2y** and **2z**) and thioethers (**2ac**) were tolerated as well, with no adverse effects on regioselectivity or catalyst poisoning (*38*). The reaction of an *N*-aryl amine (to **2ag**), however, was unsuccessful under these conditions, and the starting material was returned unchanged (*39*).

Having demonstrated that the reaction works well on heavily substituted secondary amines, we next sought to investigate the process with less hindered substrates. These types of amines would be expected to form stable bis(amine)-Pd(II) complexes (compare with **int-V**, Fig. 3C), and their high nucleophilicity suggested that selective attack on the putative Pd anhydride complex might be difficult to control. Additionally, each substrate contains up to four C–H bonds that can readily undergo β-hydride–elimination side reactions. Despite these potential pitfalls, we found that a range of amines with three substituents worked very well in the C–H carbonylation (**2ah** to **2aq**) when the reaction was conducted using phenylbenzoquinone, a hindered variant of BQ that prevents deleterious oxidative amination of the quinone scaffold. A substrate with only unfunctionalized alkyl groups worked well (**2ah**), demonstrating that the success of the reaction is not the result of remote functionality influencing the reactivity. A variety of functional groups on the amine substituents were tolerated, including sulfones (**2aj**), esters (**2ak**), aromatic heterocycles (**2al**), and alkenes (**2an**), producing the β-lactams in high yields. Aliphatic heterocycles were also competent substrates for this reaction (**2aq**), thereby providing a simple method by which to functionalize readily available amine building blocks suitable for complex molecule synthesis. Our C–H carbonylation even produced unsubstituted β-lactam products from unbranched secondary amines, albeit in lower

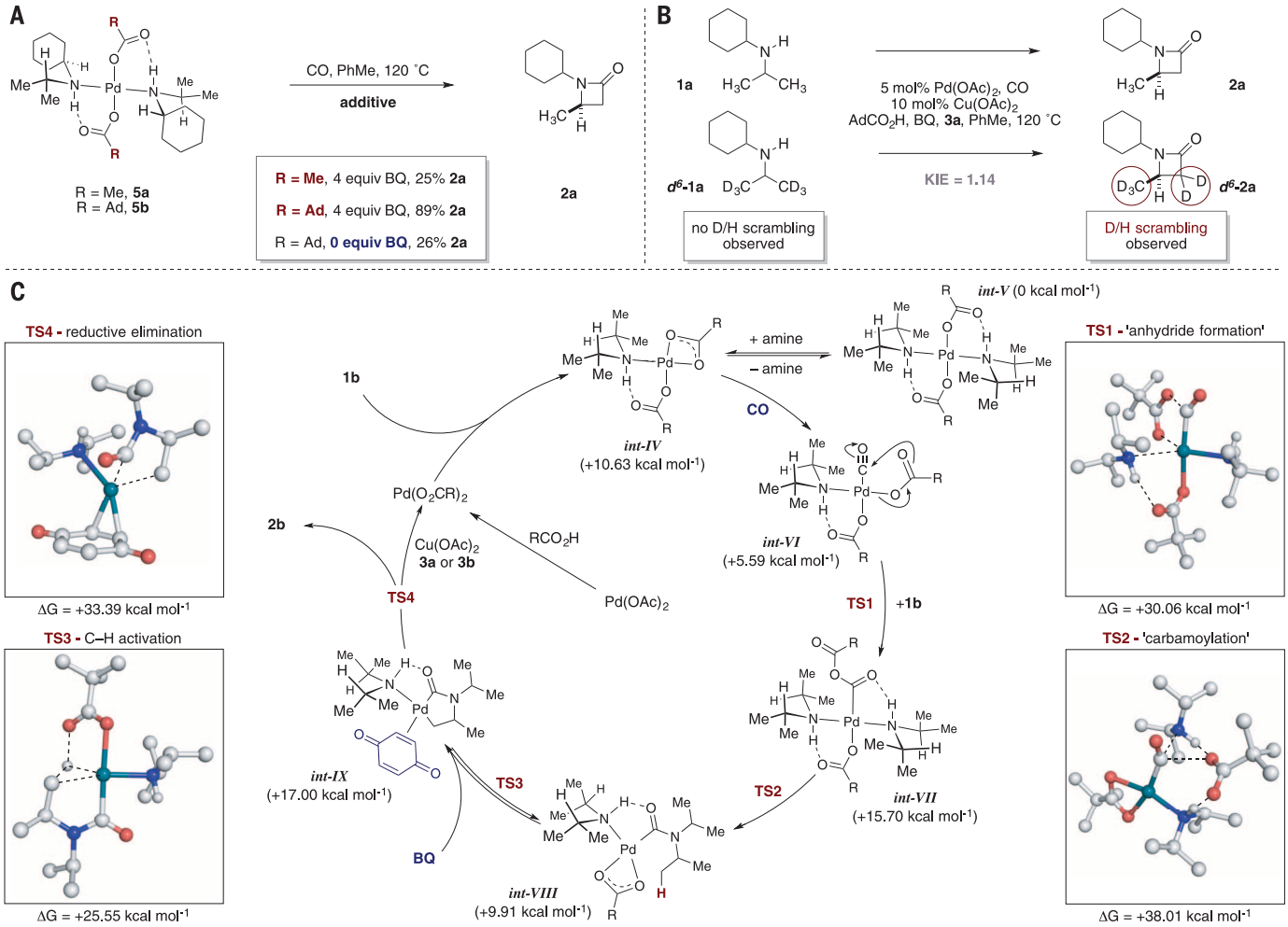


Fig. 3. Mechanistic evaluation of the C–H carbonylation reaction. (**A**) Stoichiometric studies. (**B**) Kinetic isotope effect (KIE) studies. (**C**) Proposed mechanism for C–H carbonylation of aliphatic amines. In the insets, blue is nitrogen, teal is palladium, red is oxygen, and light gray is carbon. Dotted lines indicate breaking and forming bonds. Computational studies were conducted as in Fig. 2.

yields (due in part to by-products formed from *N*-acylation and β-hydride elimination) compared with those from the other amine types (**2ar** to **2as**). As a whole, our scope studies demonstrate that the C–H carbonylation reaction tolerates a wide range of synthetic versatile functional groups spanning more than 40 examples, highlighting the generality of this transformation.

Application to complex molecules

Aliphatic amine motifs are present in at least 30% of small-molecule pharmaceutical agents and are heavily represented in preclinical candidates (*40*). Therefore, a major benefit of our aliphatic amine C–H carbonylation process is its potential amenability to mid- and late-stage functionalization applications (*41*). In more complex molecules, the competition between numerous Lewis basic functionalities capable of steering C–H activation could cause deactivation or selectivity issues.

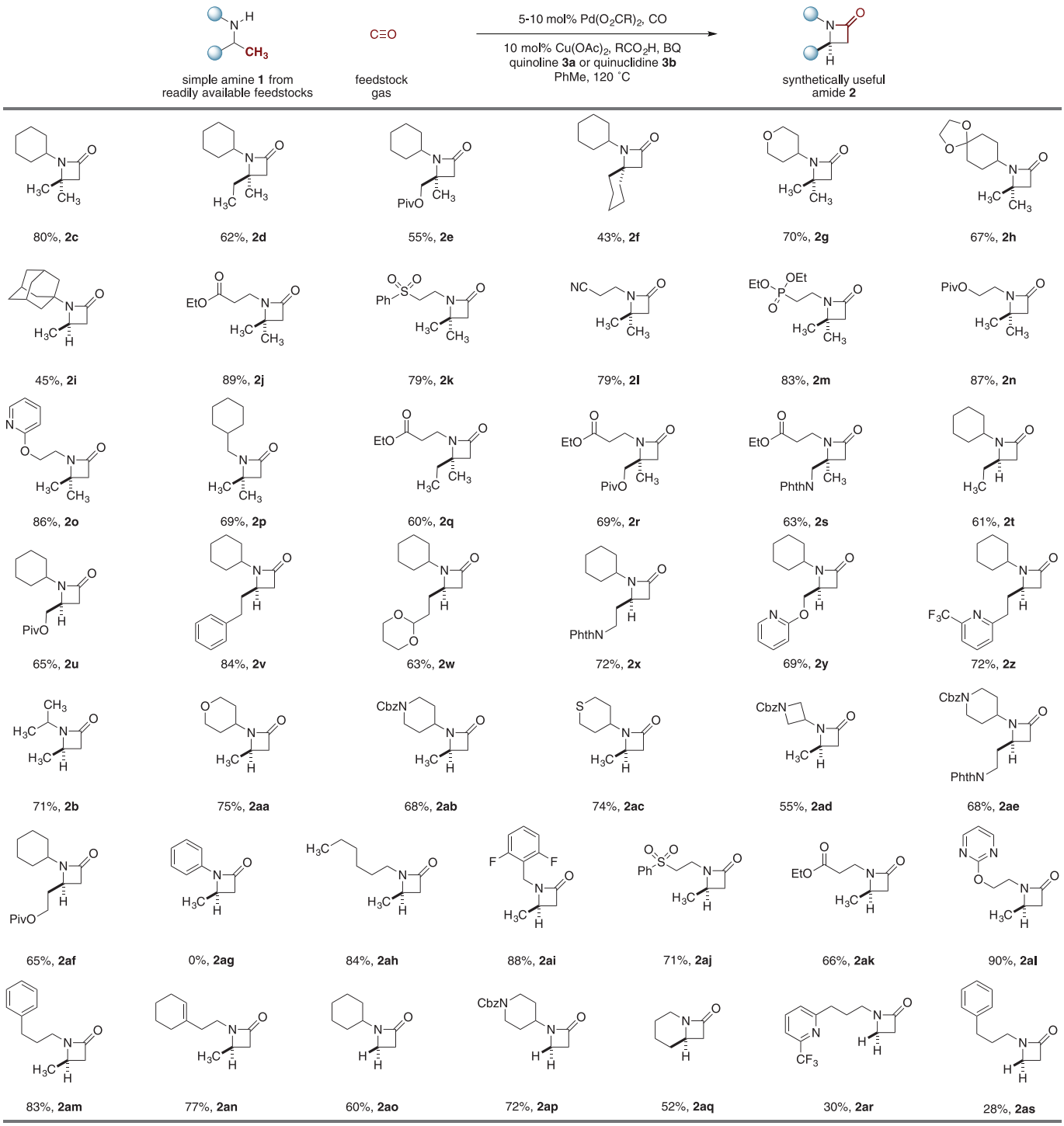


Fig. 4. The scope of the aliphatic amine C–H carbonylation. Yields of isolated products are shown. All compounds are racemic. Piv, pivaloyl group; Et, ethyl group; Phth, phthalimido group; Cbz, carbobenzyloxy group.

To test this, we prepared an amine (**1at**) with three possible sites of C–H activation and found that C–H carbonylation was directed by the aliphatic amine motif (to form **2at**) without any trace of the competitive pyridine-directed C–H activation product (Fig. 5A). To further the potential for late-stage functionalization, we subjected a selection of pharmaceutical derivatives and biologically active molecules to our C–H carbonylation protocol (Fig. 5B). Salbutamol and propranolol are β_2-adrenergic receptor agonists and are representative of a huge range of marketed pharmaceutical agents with a distinctive secondary amino alcohol. Simple derivatives of these molecules (**6a** and **6b**) effectively underwent C–H carbonylation to form β-lactams (**7a** and **7b**) in synthetically useful yields. A derivative of the acute heart failure drug dobutamine (**6c**) reacted smoothly to afford β-lactam in 72% yield (**7c**). Fenfluramine (**6d**), part of an anti-obesity treatment, was successfully carbonylated to yield a separable mixture of regioisomeric β-lactams (**7d**, 2.5:1), highlighting a moderate selectivity for the branched methyl group. Last, C–H carbonylation on the aza-sterol **6e**, an inhibitor of the hedgehog-activating transmembrane protein Smoothened (*42*), formed the β- lactam **7e** in useful yield, providing access to valuable analogs of this molecule that would be difficult to obtain by other means. A successful late-stage functionalization program would require the delivery of multiple analogs to get the maximum benefit from the strategy; β-lactams support a rich array of chemistry that can transform the amide function into pharmaceutically relevant motifs (*43*). Removal of the hydroxyl-protecting group from β-lactam **7b** yielded alcohol **8**, reductive ring opening afforded β-amino alcohol **9**, and esterification yielded β-amino ester **10** (Fig. 5C). Under certain reductive conditions, the β-lactam could be transformed into azetidine **11**, an important structural feature that is common in many drug development programs (Fig. 5C), underlining the diversity of structural motifs readily available from this aliphatic C–H activation tactic.

Outlook

We expect this general C–H carbonylation process for aliphatic secondary amines to find broad application among practitioners of synthetic and pharmaceutical chemistry. In addition to the utility of this protocol, we anticipate that the distinct reactivity of free-NH aliphatic amines in combination with Pd catalysts will inspire further advances in a range of C–H activation processes. Moreover, this C–H carbonylation pathway is conceptually distinct from classical cyclopalladation-related approaches and may lead to opportunities for C–H activation reactions in other classes of functionalized aliphatic and aromatic molecules.

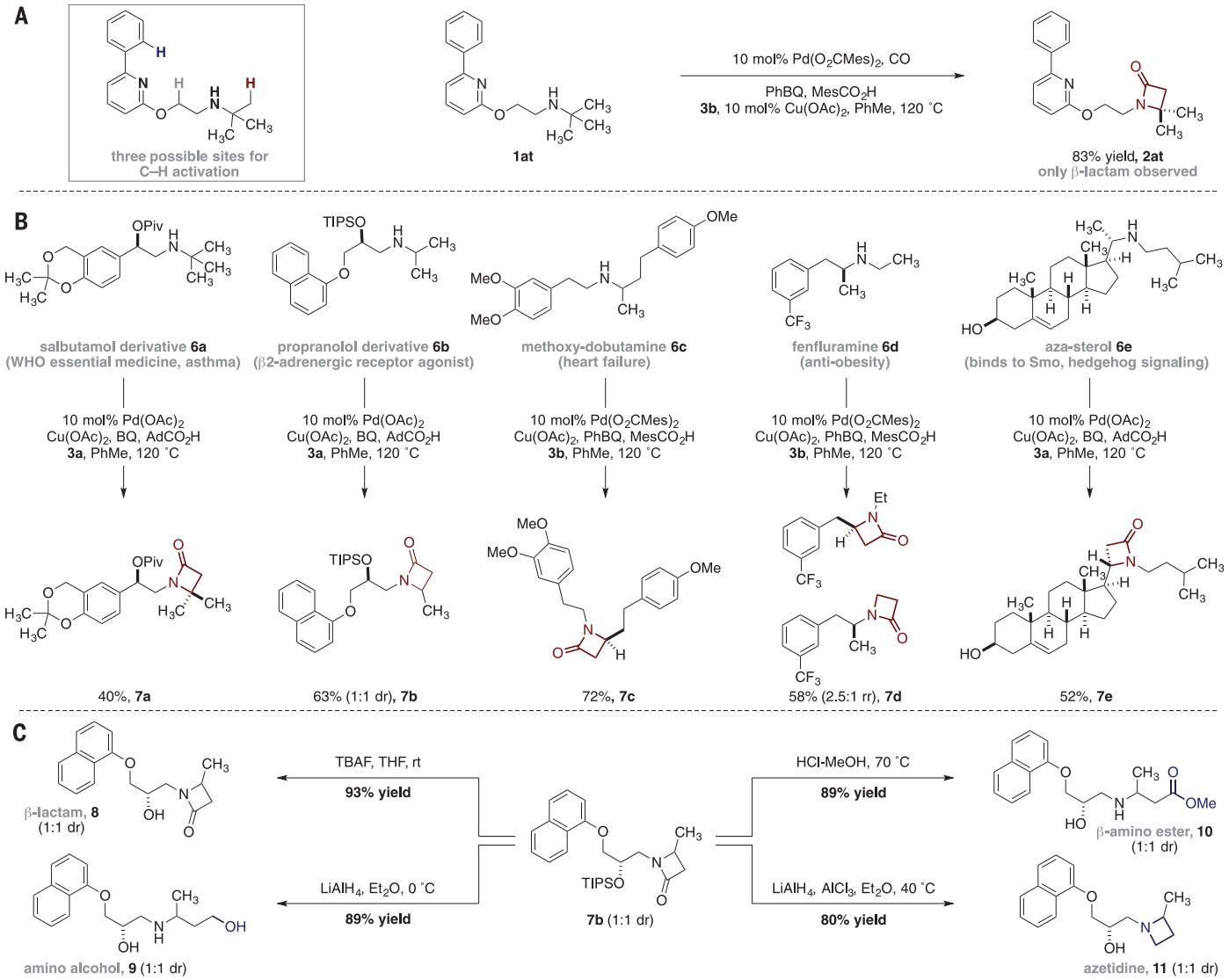


Fig. 5. Application to complex substrates. (**A**) Regioselective C–H activation in the presence of competing directing groups. (**B**) Late-stage C–H functionalization on biologically active molecules. (**C**) Derivatizations of the β-lactam framework. TIPS, triisopropylsilyl; WHO, World Health Organization; Smo, Smoothened (protein); TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; dr, diastereoisomeric ratio; rr, regioisomeric ratio; rt, room temperature.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/354/6314/851/suppl/DC1
Materials and Methods
Figs. S1 to S3
NMR Spectra
References (*44*–*55*)

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PLANT SCIENCE

Improving photosynthesis and crop productivity by accelerating recovery from photoprotection

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Crop leaves in full sunlight dissipate damaging excess absorbed light energy as heat. When sunlit leaves are shaded by clouds or other leaves, this protective dissipation continues for many minutes and reduces photosynthesis. Calculations have shown that this could cost field crops up to 20% of their potential yield. Here, we describe the bioengineering of an accelerated response to natural shading events in *Nicotiana* (tobacco), resulting in increased leaf carbon dioxide uptake and plant dry matter productivity by about 15% in fluctuating light. Because the photoprotective mechanism that has been altered is common to all flowering plants and crops, the findings provide proof of concept for a route to obtaining a sustainable increase in productivity for food crops and a much-needed yield jump.

According to detailed forecasts of future global food demand, current rates of increase in crop yields per hectare of land are inadequate. Prior model predictions have suggested that the efficiency of the photosynthetic process and thereby crop yield could be improved (*1*). Here, we show improvement of photosynthetic efficiency and crop productivity through genetic manipulation of photoprotection.

Light in plant canopies is very dynamic, and leaves routinely experience sharp fluctuations in levels of absorbed irradiance. When light intensity is too high or increases too fast for photochemistry to use the absorbed energy, several photoprotective mechanisms are induced to protect the photosynthetic antenna complexes from overexcitation (*2*). Excess excitation energy in the photosystem II (PSII) antenna complex can be harmlessly dissipated as heat, which is observable as a process named nonphotochemical quenching of chlorophyll fluorescence (NPQ) (*3*). Changes in NPQ can be fast but are not instantaneous and therefore lag behind fluctuations in absorbed irradiance. In particular, the rate of NPQ relaxation is slower than the rate of induction, and this asymmetry is exacerbated by prolonged or repeated exposure to excessive light conditions (*4*). This slow rate of recovery of PSII antennae from the quenched to the unquenched state implies that the photosynthetic quantum yield of CO_2 fixation is transiently depressed by NPQ upon a transition from high to low light intensity (Fig. 1). When this hypothesis was tested in model simulations and integrated for a crop canopy over a diurnal course, corresponding losses of CO_2 fixation were estimated to range between 7.5 and 30% (*5*–*7*). On the basis of these computations, increasing the relaxation rate of NPQ appeared to be a very promising strategy for improving crop photosynthetic efficiency and in turn yield (*8*).

Although the exact NPQ quenching site and nature of the quenching mechanisms involved are still debated (*9*), it is clear that for NPQ to occur, PSII-associated antennae need to undergo a conformational change to the quenched state,

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